



Potential Neurological Outcomes in COVID-19 Patients: A Non-systematic Review of the Literature During the First Year of the COVID-19 Pandemic

COVID-19'lu Hastalarda Potansiyel Nörolojik Sonuçlar: Pandeminin İlk Yılında Literatürün Sistemati Olmayan Bir Derlemesi

© Khadija Asif¹, © Farhat Abbas²

¹Faisalabad Medical University, Allied Hospital, Unit of Medicine I, Department of Medicine, Faisalabad, Pakistan

²Faisalabad Medical University, Allied Hospital, Unit of Medicine II, Department of Medicine, Faisalabad, Pakistan

Abstract

Coronavirus emerged from Wuhan China, which has been a global challenge for healthcare authorities and individuals. Patients are presenting to clinicians with neurological symptoms caused by coronavirus disease-2019 (COVID-19) or with preexisting neurological conditions with fear of contracting the virus. This is a literature review of COVID-19 patients and patients with underlying neurological conditions affected by the pandemic encompassing December 2020 to March 2021. 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 symptoms were reported. According to recently published literature, some of the patients with coronavirus who have respiratory symptoms also develop neurological symptoms. Certain medical emergencies such as stroke require immediate treatment to ensure better clinical outcomes for the patients. Neurologists and clinicians need to recognize these acute symptoms in order to timely manage and treat the affected patients.

Keywords: Coronavirus, manifestations, neurology, SARS-CoV

Öz

Sağlık otoriteleri ve bireyler için küresel bir meydan okuma olan koronavirüs, Çin'in Wuhan kentinde ortaya çıktı. Hastalar, koronavirüs hastalığı-2019'un (COVID-19) neden olduğu nörolojik semptomlarla veya virüse yakalanma korkusuyla önceden var olan nörolojik bozukluklarıyla klinisyene başvurmaktadır. Bu çalışma sistematik bir derleme olmasa da, COVID-19'lu hastalardaki ve alta yatan nörolojik bozuklukları olan hastalardaki nörolojik sonuçları araştıran, Aralık 2020 ile Mart 2021 arasında yapılan bir literatür derlemesidir. Koronavirüsten muzdarip hastaların nörolojik belirtileri hakkında veriler için PubMed, Google Scholar, EBSCO, Semantic Scholar ve Wiley Online dahil olmak üzere birden fazla veritabanını taradık. Hastaların klinik verileri ve komorbiditeleri incelendi. Baş ağrısı, baş dönmesi, hipozmi ve inme bildirilen semptomlar arasındaydı. Gelişmekte olan literatür, koronavirüs ile enfekte hastaların solunum semptomları ile birlikte nörolojik semptomlar da yaşadığını gözler önüne sermektedir. İnme gibi bazı tıbbi acil durumlar, hastaları kurtarmak için acil tedavi gerektirir. Nörologların ve klinisyenlerin, hastaları zamanında yönetmek ve tedavi etmek için bu semptomları tanıması gerekir.

Anahtar Kelimeler: Koronavirüs, belirtiler, nöroloji, SARS-CoV

Introduction

In December 2019, a market in the city of Wuhan, Hubei, China marked the beginning of the novel coronavirus infection which was identified from cases of pneumonia with an unknown pathogen (1). Initially, the viral infection was disseminating in China, leading them to impose precautionary measures to control

the virus. However, the virus started to spread outside China, and as of now, has overwhelmed almost all countries. On 11th March 2020, the World Health Organization declared novel coronavirus infection as a pandemic and has been guiding the world health community on necessary precautionary measures ever since (2). With the rapid spread of coronavirus disease-2019 (COVID-19), both individuals and health authorities came under great pressure,

Address for Correspondence/Yazışma Adresi: Khadija Asif MD, Faisalabad Medical University, Allied Hospital, Unit of Medicine I, Department of Medicine, Faisalabad, Pakistan

Phone: +92 3023302300 E-mail: dr.khadija.asif@outlook.com ORCID: orcid.org/0000-0002-9914-2492

Received/Geliş Tarihi: 12.05.2021 **Accepted/Kabul Tarihi:** 31.07.2022

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Turkish Journal of Neurology published by Galenos Publishing House.

and both parties took action to control and protect themselves and society. Many studies have suggested that the possible origin of coronavirus is bats and that, the virus has transmitted from bats and then infected mammals (3). Coronavirus infects many organ systems of the body including the central nervous system (CNS) and hepatic, cardiovascular, and respiratory systems (4). Primary physical effects of the novel coronavirus are in the respiratory system, but nervous system involvement has also been reported in patients (5).

Primarily, the route of transmission of coronavirus is through respiratory droplets by close and direct human to human contact (6). Although symptoms of the infected person are commonly fever, dry cough, sore throat, and myalgia; some patients may also experience neurological or gastrointestinal tract symptoms (7). Individuals, particularly the elderly and those with underlying comorbidities, are more prone to develop a serious infection as well as death (8). On the other hand, young individuals without any comorbidities are also facing morbidity and mortality due to COVID-19 infection (9). A major hurdle in controlling this virus is identifying those people who are infected but remain asymptomatic and are disseminating the disease.

Coronavirus genome has 4 genera consisting of alpha, beta, gamma, and delta, and it is a single-stranded positive-sense RNA virus (10). One of the key topics regarding coronavirus has been its pathogenesis. Many studies have made suggestions about the mode of action of coronavirus in the human body. After entering the human body severe acute respiratory syndrome coronavirus (SARS-CoV) initiates its actions by binding to angiotensin-converting enzyme 2 (ACE2), this has been suggested to be its primary mode of action (10). SARS-CoV also uses protease TMPRSS2 for S-protein priming. In humans, ACE2 receptor is expressed in the airway epithelium, kidneys, lung parenchyma, vascular endothelium, and the CNS. Some reports have put forward the potential of SARS-CoV to invade the CNS to initiate SARS-CoV manifestations (11). Although the damage caused by this virus has been reported in COVID-19 patients with different symptoms, the extent of the damage has not yet been discovered.

Studying the effects of novel coronavirus on CNS can open doorways to patients suffering from its effects, and help in formulating effective treatment modalities.

Methodology

In this literature review (December 2020 to March 2021), we used multiple databases such as PubMed, Google Scholar, EBSCO, Semantic Scholar, and Wiley Online with the snowballing technique. A total of 1,508 articles were found using the following generic terms: "Coronavirus", "COVID-19" and "Neurology". The extracted articles were screened by: a) Title, b) Authors, c) Abstract, d) Journal, e) Main text, f) Article type, and g) Publication date. Articles related to coronavirus infection with neurological symptoms were included. Articles not related to the topic, not written in English and not published in a journal were excluded.

Pathogenesis of SARS-CoV in CNS

As mentioned earlier, SARS-CoV exerts its effect mainly by binding to ACE2 receptors (12). CNS has these receptors, thereby, some infected individuals may experience CNS symptoms (13). Although some studies report that the mere presence of these receptors does not necessarily mean that the virus is going to invade the particular organ system (14). Previously, certain studies

suggested that some patients with SARS-CoV had the virus exclusively in neurons (15). ACE2 receptors are also present in glial cells and spinal neurons, where the virus can multiply to damage these cells. Some studies have suggested that the primary route of invasion of the CNS by the coronavirus is the olfactory bulb (16). Through the olfactory bulb, the virus spreads to other parts of the brain such as the thalamus and the brain stem. ACE2 receptors are strongly expressed in two other areas of the brain responsible for the regulation of the respiratory cycle; ventrolateral medulla and nuclei of the tractus solitarius (17). Prior studies have suggested that when SARS-CoV invades the CNS, it induces direct neural death in the respiratory center of the medulla by upregulation of interleukin-6 (IL-1), IL-6, tumor necrosis factor (TNF)-alpha, and initiating an inflammatory response (18). An emerging hallmark of the coronavirus is coagulopathy, whereby "sepsis-induced coagulopathy" occurs in patients with a hypercoagulable state and predisposes them to clinical presentations like stroke (19).

Neurological Damage Ensued by COVID-19

A neurological damage mechanism of SARS-CoV is the, entry of the virus into the cerebral circulation and its sluggish forward movement. Once the virus is in the neuronal tissues, interaction with the ACE2 receptors commences its action (13). Additionally, since the virus gains entry through the olfactory route, hyposmia has been noted in some patients (20). Moreover, immunological damage to CNS is initiated by the cytokine storm whereby novel coronavirus induces the innate immune system in the host to release cytokines such as IL-1, IL-6, and TNF-alpha. This produces an inflammatory response which damages the neuronal tissues (21). This cascade of infection and inflammation leads to brain hypoxia causing further damage (22). Lastly, pneumonia caused by the coronavirus further aggravates hypoxic brain injury.

Neurological Symptoms of Patients with COVID-19

Various symptoms experienced by patients with COVID-19 have been reported in the literature. Patients with COVID-19 have neurological symptoms such as headache, myalgia, confusion, and dizziness (23). Hyposmia and dysgeusia has been reported as well (24,25,26). Mao et al. (27) reported that some of the patients also suffered from cerebrovascular diseases including ischemic stroke and cerebral hemorrhage. Common neurological manifestations of COVID-19 are listed in Table 1.

Table 1. Common neurological presentation of COVID-19

	Manifestations
Location	Headache
	Dizziness
	Cerebrovascular disease
Central nervous system	Epilepsy
	Encephalopathy
	Ataxia
	Hypogeusia
Peripheral nervous system	Hyposmia
	Neuralgia
COVID-19: Coronavirus disease-2019	

Central Nervous System Manifestations

1. Stroke

Stroke as a medical emergency can occur in patients with COVID-19 (28). Furthermore, stroke occurs in both young and old patients with COVID-19 (29). A putative mechanism that may predispose a person to stroke is hypercoagulation and sepsis induced coagulopathy associated with COVID-19 (19). A study reported that stroke was more commonly associated with COVID-19 patients suffering from a severe infection, which further contributed to 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 COVID-19 (30). Patients with stroke and COVID-19 are reported to have abnormal leukocyte counts and increased blood levels of CRP, D-dimer and ferritin in laboratory tests (31).

2. Seizures

Many studies have reported seizures in patients suffering from coronavirus. Initially, patients with COVID-19 presented only with respiratory symptoms, but later on developed complications such as seizures (32,33,34).

3. Encephalitis

The first patient with COVID-19 who suffered from encephalitis was reported from Japan (35). This patient had neck stiffness and her cranial computed tomography scan was normal. The mechanism by which SARS-CoV may lead to encephalitis is direct viral invasion and binding to ACE2 receptors through the blood-brain barrier (33). It can be postulated that patients who suffer from severe COVID-19 infection are predisposed to neurological complications.

4. Encephalopathy

Encephalopathy occurs in patients suffering from severe COVID-19 (36). It has been suggested that disseminated intravascular coagulation and venous thromboembolism caused by COVID-19 may cause encephalopathy (37). The first case report of an elderly patient suffering from COVID-19 and encephalopathy was published on 21-03-2020 (38) from China, it was also reported that some of the patients experienced hypoxic encephalopathy (39). Furthermore, patients with acute necrotizing encephalopathy were reported and the mechanism was postulated to be a cytokine storm releasing large amounts of cytokines that cross the blood-brain barrier and damage the neural parenchyma (40). Lastly, individuals suffering from encephalopathy may also be predisposed to suffer strokes (41).

5. Dizziness and Headache

Dizziness and headache have been regarded as the most common neurological symptoms in COVID-19 patients (27,42,43). The release of cytokines and chemokines from the macrophages may be associated with COVID-19 headache (44). Although the commonality of these symptoms are clearly stated, the exact pathophysiology and mechanism are still not understood.

Peripheral Nervous System Manifestations

1. Anosmia and Hypogeusia

Anosmia and hypogeusia are reported to be the common and initial neurological manifestations in patients with COVID-19, and they may even occur before respiratory symptoms (34,45). In a study, nearly a quarter of the patients reported anosmia with improvement occurring after one week (45). The virus primarily enters into the cerebral circulation by passing through the olfactory bulb. This has been known to cause a disturbance in the smell sensation of the host. Studies further report that some of the patients may only experience hyposmia/anosmia and should self-isolate (20).

2. Skeletal Muscle Injury

Although less common, skeletal muscle involvement is one of the neurological symptoms of COVID-19 (46). In China, A 79-year-old man was admitted to the Hubei Provincial Hospital of Traditional Chinese Medicine due to right limb weakness for 1 day and slight cough for 1 week. The patient was treated with antiviral and anti-inflammatory drugs with supportive care until his discharge. Clopidogrel 75 mg/day and atorvastatin 20 mg/day were administered orally to treat acute ischemic stroke. After 12 days of treatment, he could walk normally and communicate almost fluently (47).

Special Care for Patients with Underlying Neurological Conditions

Many patients, particularly those who are older than 65 years with co-morbidities are more anxious and stressed from fear of contracting viral illnesses and suffering from severe infection. Mortality rates are higher in this age group, therefore special care and support should be offered to these patients.

Multiple Sclerosis (MS)

Patients with MS use drugs that may predispose them to contract the virus more rapidly and suffer from severe infection as compared to healthy individuals. Currently, no consensus has been reached whether MS patients are more susceptible for contracting COVID-19 or should MS treatment be modified during the pandemic (48). Furthermore, a precise mechanism by which MS patients develop coronavirus infection is yet to be determined (49). Recently, a study reported adamantanes being successfully used in MS patients without changing their neurological functional status (50).

Parkinson's Disease (PD)

During the pandemic, clinical visits of PD patients are suspended since outpatient visits lead to increased stress and confusion amongst them. It was reported that some of the patients developed psychiatric symptoms such as hallucinations, anxiety and psychosis (51). Generally, patients inquire about COVID-19 pathology and their susceptibility of contracting the virus. Currently, a definitive association between the two pathologies has not been shown (52). Additionally, it has been suggested that patients with PD with restricted lung capacity due to axial akinesia are predisposed to COVID-19 infection (53). Lastly, the correlation between PD and COVID-19 is currently unknown, but the situation has generated ample stress among PD patients (54).

Epilepsy

Current practice is; to keep patients with epilepsy out of the hospitals in order to avoid COVID-19 infection and to provide home-based care (55). Except a few, none of the drugs used for epilepsy treatment are immunosuppressant, therefore they would not increase the chance of contracting COVID-19. Patients with epilepsy are not more prone to contract COVID-19, and are less likely to suffer from severe COVID-19 infection (56).

Neuromuscular Disorders

Patients with neuromuscular disorders are often treated with immunosuppressive drug(s), which increase(s) their chances of contracting the virus.

Also, patients suffering from myasthenia gravis and Lambert-Eaton syndrome may have weakness in their respiratory muscles, which may predispose them to develop complications if they become infected with the new coronavirus. Those on immunosuppressive drugs should be extra-cautious and maintain social distancing more vigilantly (57).

Conclusion

Currently, the whole world is in the grip of the new coronavirus. Knowledge about the neurological manifestations of COVID-19 is increasing and physicians should seek these symptoms for proper and timely management of patients.

Timely and early detection of symptoms not only reduces morbidity but also ensures smooth recovery of patients. In addition, novel information from laboratory studies, pathophysiology and treatment options should be sought for ensuring better recovery of patients.

Knowledge of the above-mentioned parameters will help neurologists, scientists, and clinicians best treat their patients.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: K.A., Design: K.A., Data Collection or Processing: F.A., Analysis or Interpretation: K.A., F.A., Literature Search: K.A., F.A., Writing: K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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