

Review Paper: Neuromuscular Problems in the Patients With COVID-19: A Review Study



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ABSTRACT

Purpose: SARS-CoV-2 is a member of the betacoronavirus genus that primarily targets the human respiratory system and causes pneumonia-like symptoms. This article aims to review neuromuscular problems in patients with COVID-19 based on the available evidence and possible consequences.

Methods: This narrative review study gathered the related and newest studies published (without time limitation) about the neurological impairment of the coronavirus.

Results: The studies showed that the patients with COVID-19 show a variety of respiratory symptoms and neuromuscular and neurological symptoms. The neurological symptoms associated with the underlying disease include headache, dizziness, disturbance of consciousness, ataxia, manifestations of epilepsy, stroke, peripheral nerve injury (like hypoadomia, hyposemia, neuralgia). The findings of this review study also reveal that there are a variety of neuromuscular symptoms in the affected patients. Besides, some specific changes in these symptoms have occurred since the emergence of this epidemic.

Conclusion: Neurologists should pay more attention to the possible signs of direct and indirect involvement of the nervous system and its lasting effects, which might have been ignored in the acute phase of the disease.

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Highlights

- COVID-19 was found in the brain.
- COVID-19 infection causes neuromuscular clinical problems and complications in addition to the commonly known respiratory symptoms.
- Up to one-third of patients with COVID-19 show at least one neurological symptom.
- Most central nervous problems due to COVID-19 are headache, acute ischemic stroke and cognitive impairment.
- Most peripheral nervous problems due to COVID-19 are myalgia and muscle fatigue.

Plain Language Summary

COVID-19 infects the brain and cause some neurological and neuromuscular problems such as headache, stroke, myalgia and fatigue.

1. Introduction

Coronaviruses are a group of viruses that cause mild to severe respiratory disorders in the affected patients. These symptoms include fever, dry cough, shortness of breath, nasal congestion, sore throat, nausea, vomiting, myalgia, arthralgia, fatigue (muscular and mental), joint swelling (as reactive arthritis), headache, diarrhea, and rarely arthritis. It should be noted that these viruses can also cause mild or severe diseases in various systems of the body, such as the respiratory system, digestive system (intestines and liver), musculoskeletal system (muscles and joints), and nerves. Although it was initially suggested that the coronavirus is present in the respiratory tract of the infected people, it has also been recently recognized in the patients' brains as well. In this regard, various methods such as immunohistochemistry, electron microscopy, and real-time reverse transcription-PCR have been used to detect the presence of coronavirus in the brain [1].

Recent reports from the worst affected countries such as China, South Korea, Italy, and Spain suggest that there are other neuromuscular clinical problems and complications in addition to the commonly known respiratory symptoms. Some of these symptoms include posterior reversible encephalopathy syndrome, myopathy or neuropathy in acute respiratory distress syndrome, neuromuscular problems with contracture and plantar flexor ulceration, and mental health problems [2].

The current data suggest that the COVID-19 virus also affects the Central Nervous System (CNS). Some studies categorize the neurological symptoms associated with COVID-19 into three groups: neurological symptoms associated with underlying diseases (headache, dizziness, impaired consciousness, ataxia, manifestations of epilepsy, and stroke), symptoms of peripheral nerve injury (hypoadomy, hyposmia, neuralgia), and symptoms of skeletal muscle injury, that are often associated with liver and kidney damage [3]. A study in Wuhan, China, indicated the neurological manifestations in more than one-third of the infected patients (36.4%) who had more severe neurological symptoms such as acute brain disease, impaired consciousness, and skeletal muscle injury [4]. Accordingly, a significant increase in the number of vascular events such as ischemic strokes and thrombosis have been reported due to the COVID-19 virus effect on the coagulation mechanisms [5]. However, it is unclear whether the primary cause of neurological syndromes is the direct effect of the SARS-CoV-2 virus entering the central nervous system or the indirect response of the body as a cytokine storm [3].

A wide range of cognitive and psychological disorders have been reported in patients, including mood swings (depression), anxiety, suicide, organic hallucinations (vision and hearing), behavioral disorders, delirium, harassment, lack of real time and place recognition, hypomanic disorder, and so on [6]. Some studies have also referred to the coronavirus neurotropic invasion pathway, suggesting olfactory-hematogenous pathways, trans-neuronal machinery, and lymphatic pathways as major pathways for coronaviruses to enter the CNS [7]. According to the

evidence, these viruses, initially thought to be respiratory pathogens, can affect the nervous system (neurotropic), attack the nervous system (neuroinvasive), or even severely affect the nervous system (neurovirulent). In other words, these viruses can affect normal neural structures and functions [1, 8]. Therefore, the purpose of this article is to review the evidence of neuromuscular problems in patients with COVID-19 based on the available evidence.

Neurological manifestation of the patients with COVID-19

Viruses are the most common pathogens detected in the respiratory tract. It is estimated that about 200 different viruses can infect human airways. Therefore, respiratory viral infections are common worldwide; they are considered a significant problem for human and animal health [9]. Some respiratory viruses, such as the human common cold virus, regularly circulate the world each year [10]. However, from time to time, new respiratory viruses appear and cause viral epidemics with more serious symptoms such as neurological disorders [11]. These bizarre events usually occur when RNA viruses such as influenza A, human coronaviruses such as MERS-CoV and SARS-CoV, or henipaviruses present in animals (as a reservoir) enter new hosts. Then, they can cause adverse consequences, especially neurological ones, which increases the rate of complications [12-14].

Outbreaks of COVID-19 have already been reported in most countries. This epidemic has been spread worldwide at a high rate and transmitted from human to human [15, 16]. The main symptoms of COVID-19 include fever, dry cough, and fatigue [16]. As a result of persistent or latent acute viral infections, the CNS is not immune to the changes that lead to neurological diseases, although the same system maintains life and coordinates homeostasis through a series of amazing complex cellular and molecular interactions. The CNS viral infections occur rarely, but they are difficult to be assessed at the clinical level. For instance, viral encephalitis is one of the most common viral diseases [7].

Scientific reports show that several respiratory viruses can attack the nervous system [17]. The same viruses can spread from the respiratory tract to the CNS, causing various diseases, including encephalitis and long-term neurological diseases. Like other human viruses invading the CNS, respiratory viruses can damage the CNS through indirect host immune responses [17]. Although, the etiological cause of many neurological disorders is still unclear, opportunistic respiratory pathogens in humans may be associated with the stimulation or exacerbation

of these neurological disorders [7]. Notably, physicians have found that some patients with COVID-19 do not display the usual respiratory symptoms such as fever and cough at the time of diagnosis [4]. Instead, some patients manifest only minor neurological symptoms such as headache, lethargy, unsteady gait, and weakness, which may be due to nonspecific manifestations of COVID-19 or secondary cerebral hemorrhage, stroke, and other reported neurological diseases [18]. However, the physiological relationship between COVID-19 and the occurrence of cerebral hemorrhage is still unclear, and it is only assumed, based on the available evidence, that COVID-19 may cause intracranial hemorrhage [19].

One study examined 214 patients with COVID-19; 78 patients (36.4%) displayed neurological manifestations such as headache, dizziness, acute brain disease, and impaired consciousness, and 40 patients (18.7%) required Intensive Care Unit (ICU) interventions due to severe involvement of the nervous system [4]. Different patients display different neurological problems and symptoms so that they might have headache, dizziness, impaired consciousness, ataxia, manifestations of epilepsy, olfactory, taste, or vision impairments, short-term dementia, hypo-ageusia, hyposmia, neuralgia, cognitive or mental disorders, and so on [2-4, 7, 18]. Therefore, understanding the mechanisms of how the virus acts on the central nervous system is essential. First, it helps better understand the pathological consequences of virus infection, and second it helps design new diagnostic and intervention strategies [6, 7].

Mechanism of nervous system involvement in the COVID-19

Attacking the nervous system is a common mechanism of coronaviruses [17]. Given the high similarity between SARS-CoV and SARS-CoV2 [20], it is quite possible that SARS-CoV-2 acts the same as SARS-CoV. Therefore, knowing the involvement of the nervous system in the virus attack is essential to manage, prevent, and treat the respiratory failure caused by SARS-CoV2 [21]. SARS-CoV2 is mainly considered a respiratory pathogen, but it has also been found in the brains of the infected patients, indicating that this virus can affect the normal neural structures and functions [22]. Various methods have been applied to detect the presence of coronavirus in the brain, such as immunohistochemistry, electron microscopy, and real-time reverse transcription-Polymerase Chain Reaction (PCR) [1]. Some studies have referred to the coronaviruses' mechanisms and pathways to attack the nervous system, suggesting that olfactory-hematoge-

nous, transneuronal, and lymphatic pathways as coronaviruses' routes of neuroinvasion [7, 8].

The olfactory-hematogenous pathways

When the olfactory tract is the main route through which toxins reach the CNS, it is not surprising that the same tract is used as a pathway for coronavirus to invade the human CNS. In both HCoV-OC43 and SARS-CoV, which are very similar to SARS-CoV-2, infection of the nose can lead to the infection of both the respiratory tract and nervous system [23, 24]. Similarly, although the human coronavirus is more restricted to the airways, it can spread to other tissues, including the CNS [25]. Once the coronavirus reaches the respiratory tract, the virus can pass through its superficial epithelial cells and enter the bloodstream, through which it enters the CNS [26, 27]. Through blood circulation, the virus can target the Blood-Brain Barrier (BBB) of epithelial cells and blood-brain-cerebrospinal fluid of epithelial cells located in the choroid plexus ventricles of the brain or leukocytes, which act as a pathway of spread to the CNS [27]. Therefore, the new SARS-CoV-2 may invade the nervous system through hematogenous airways. Another way for the human coronavirus to attack the nervous system is directly through olfactory receptors because other viruses capable of affecting the nervous system (neurotropic), such as influenza, herpes simplex, and polio, are transmitted to the CNS along the axons of olfactory receptor neurons (olfactory epithelium) [28].

Transneuronal system

This system is another potentially identified route for the human coronavirus to attack the nervous system. In this case, the coronavirus infects peripheral neurons to invade the CNS through axonal retrograde transport [29]. The coronavirus can attack peripheral nerve terminals and then reaches the CNS through synapses [30].

Lymphatic system

The lymphatic system is another possible way for the coronavirus to attack the nervous system [31]. Although the exact mechanism is still unknown, various strains of the coronavirus, such as SARS-CoV, can infect the cells involved in the internal immune system. Through these cells, they can spread to several tissues, including the CNS. Thus, the evidence suggests that these viruses, though initially are respiratory pathogens, may tend to affect the nervous system (neurotropic), invade the nervous system (neuroinvasive), or have very severe and harmful effects on the nervous system (neurovirulent) [31].

The exact route of SARS-CoV or MERS-CoV to enter the CNS has not yet been reported. However, entry through the hematogenous or lymphatic pathway, especially in the early stages of infection, seems impossible, as almost no viral particles have been detected in non-neuronal cells of infected areas of the brain [32-34]. On the other hand, increasing evidence suggests that CoVs may invade peripheral nerve terminals and access the CNS via the synaptic pathway [30, 35, 36].

Coronavirus-related neurological impairment

Some studies have referred to coronavirus-related neurological problems as Central Nervous System (CNS), Peripheral Nervous System (PNS), muscular, and behavioral impairment [1].

Central Nervous System (CNS) problems

Following infection with coronavirus, it might attack the brain and nerve tissues, causing some changes in brain structures, and create various diseases with complications and nerve cell death [1]. The pathogenesis of nervous system injury caused by COVID-19 is complex, involving a currently unknown set of interactions between viral properties, tissue sensitivity, and the host immune response [22]. The incidence of neurological features may vary between different populations [32]. After attacking the nerve tissues, the viruses can be accumulated in different brain areas such as the dorsal vagal complex, which is very important for cardiorespiratory function, basal ganglion, piriformis, and inferior limbic, and post fissure of the midbrain. Thus, sudden and severe symptoms of coronavirus infection might lead to dysfunction in these sensitive areas of the brain [23].

Human coronaviruses, including SARS-CoV and MERS-CoV, have also been detected in the brainstem, particularly the solitary nucleus and ambiguous nucleus. Examination of neuroanatomical connections and interconnections in infected animals or humans suggests that respiratory distress syndrome and death due to SARS-CoV2 infection are caused by acute dysfunction of the brainstem cardiorespiratory center [22, 37]. Among the affected areas of the brain, the medulla oblongata showed the highest rate of SARS-CoV or MERS-CoV infection [23, 24]. Netland et al. observed the infection and structural changes of the cardiorespiratory center in the medulla oblongata of SARS-CoV-infected mice [23]. Jacomy et al. reported the reduced hippocampal volume in mice with coronavirus-induced acute encephalopathy [38]. Besides, the harmful effect of this virus on the nervous system (neurovirulent) can lead to neurological

disorders and symptoms such as Multiple Sclerosis (MS) [1], meningitis and encephalitis [39, 40], stroke, seizures, encephalitis, and acroparesthesia (tingling, prickling, burning, or numb feeling in some organs) [41]. According to Kim, approximately 1.5% of patients exhibit specific neurological complications 2-3 weeks after respiratory manifestations, including impaired consciousness, paralysis, ischemic stroke, Guillain-Barre syndrome, and other neuropathies [42]. Mao also stated that up to one-third of patients with COVID-19 show at least one neurological symptom [4]. Besides, there have been several reports of neuronal deaths following coronavirus infection [34, 38, 43]. By entering the neuropilasm via Angiotensin-converting enzyme 2 (ACE-2) receptors, the coronavirus can cause neuronal death through apoptosis (programmed cell death), necrosis, and, in rare cases, autophagy (autoimmunity as a natural cell defense mechanism) [1, 38, 44].

COVID-19 can also be associated with neurological comorbidities. Acute ischemic stroke is one of the most probable severe complication of infection with COVID-19, and often occurs in the elderly. Coagulation abnormalities, such as increase in thrombocytopenia and elevated D-dimer, are often seen in COVID-19 patients. Therefore, the risks and benefits of venous thrombolysis or arterial embolectomy should be evaluated in patients with acute ischemic stroke and COVID-19. Since SARS-CoV-2 binds to the ACE-2 receptor on vascular endothelial cells, it results in abnormally increased blood pressure. Along with platelet dysfunction and blood clotting, high blood pressure abnormally increases the risk of intracranial hemorrhage in patients with COVID-19. People with neurological diseases such as amyotrophic lateral sclerosis, Parkinson disease and Alzheimer disease may also be at high risk. Similarly, patients with autoimmune diseases such as MS and myasthenia gravis are at high risk of severe COVID-19 [45].

Peripheral Nervous System (PNS) problems

The Human Coronavirus (HCoV) can also infect peripheral nerve cells and attack the CNS through axonal formations [25, 29]. It might attack the peripheral nerve terminals and then access the CNS via the synapse-connected pathway [35, 36]. Recent articles have stated that patients with SARS-CoV2 infection show neurological symptoms such as decreased sense of smell and taste and inability to speak [26]. Numerous reports have also indicated acute flaccid paralysis [40], entrapment neuropathy [46], and other neurological symptoms, including Guillain-Barre syndrome [47] as a result of coronavirus infection.

Muscular problems

Several muscle disorders and diseases have been observed in patients with coronavirus infection, including myopathy (critical illness myopathy), quadriplegia acute myopathy, myopathy with thickening of muscle fibers, and myopathy caused or associated with necrosis [48], myalgia [49], fatigue, and muscle weakness [50]. Most of these muscular dysfunctions occur due to muscle weakness during providing inpatient care in ICUs (not as a direct result of the infection) [51].

Myalgia

It is a common symptom in patients with viral infections such as new coronavirus (COVID-19) and influenza, indicating a general inflammation and cytokine response (an immune response) [52, 53]. However, COVID-19-induced myalgia is longer and more severe than those induced by other viral infections, and it may not respond to standard analgesics. Usually, when the viral load is reduced by treatment, muscle pain may also be reduced [54]. Since lactate levels increase during infection with COVID-19 (hyperlactatemia), the oxygen-carrying capacity of the blood is impaired, and the tissues become hypoxic [49]. Therefore, the pain may remain in the ischemic muscle tissue until the cause of hypoxia is eliminated through reducing the level of muscle lactate and increasing oxygen delivery to the tissues or treating the virus infection [49].

Muscle fatigue

Various muscular symptoms such as excessive muscle fatigue, palpitations, muscle pains, tingling sensations, etc., have been reported in patients with COVID-19 as complications [43, 53]. According to a report of the World Health Organization (WHO), 38% of the patients with COVID-19 develop fatigue. One study in Wuhan, China, found that this symptom is prevalent so that 70% of the patients developed fatigue [16]. However, COVID-19 is not the only cause of chronic fatigue, as it has also been reported after other viral infections like the Epstein-Barr virus [55]. Since there is no specific treatment for most viral infections, we still do not know how fatigue is developed during infection or treated after infection [50].

According to the available data, the presence of persistent viral infection in the lungs, brain, fat, or other tissues may be one of the reasons causing persistent fatigue. Besides, the prolonged and inadequate immune response of the body after clearing the infection may be another cause. Anti-inflammatory molecules have been observed in the

“cytokine storm” of patients with COVID-19, depending on the severity of the disease [56]. The cytokine storm denotes a hyperactive immune response called cytokines into the blood against virus threat in disproportionate amount or even after the virus is diminished so that it is injurious to host cells and potentially causes significant damage. Notably, the cytokine storm induced by coronavirus triggers an exaggerated inflammatory reaction, causing more damage than the coronavirus itself [56]. This condition suggests that the immune activation may follow a pattern during viral infection, which leads to the appearance of permanent symptoms in infected patients. There are just a few tips for people with chronic fatigue to manage it and save energy. They should do light mental or physical activities with regular rest intervals. Returning to work should be done gradually and in a graded process, while how to speed up daily activities is very important [50].

Cognitive impairment

Coronavirus infection is also associated with several cognitive impairments such as attention deficit, decreased memory performance [57], impaired visual-spatial abilities, impaired declarative memory, and lowered executive function [58]. According to Jacomy’s study, a reduction in the size of the hippocampus was evident in the mice infected by a human coronavirus. Then, it has been concluded that the mentioned reduction causes defects in the higher-level neural functions such as learning and memory. This finding is supported by many human studies indicating sudden changes in memory, learning, and attention before cytokine release [38]. Evidence suggests that, in a group of patients with severe COVID-19, “cytokine storm syndrome” may be developed by releasing cytokines, chemokines, and other inflammatory signals that contribute to disease progression [16, 59].

Increased inflammation can significantly damage the BBB, which in turn can strengthen the neuroinflammatory process. Neuroinflammatory activity associated with functional brain injury may partly explain the clinical cognitive decline reported in some patients during and after acute pneumonia. Changes in the level of consciousness, cognitive decline, and behavioral changes may be due to systemic inflammation associated with prolonged hypoxia and neuroinflammatory injury in specific cortical areas [60]. According to one study on patients with Acute Respiratory Distress Syndrome (ARDS), longer-term hypoxemia can be considered as a hallmark of SARS-CoV-2, which is associated with cognitive dysfunction [29, 61]. Hypoxia is associated with brain atrophy, lateral ventricular enlargement, and concomitant memory impairment [62].

Behavioral changes and mood disorder

Some changes have been observed in the mood of patients with ARDS, such as depression and nonspecific anxiety [63, 64]. ARDS is characterized by lung damage and hypoxemia, high mortality rate, and reduced life quality. Besides, it has significant cognitive and emotional complications and some specific symptoms such as mental state change, personality change, abnormal behavior, or speech and movement disorders reported with coronavirus encephalopathy [39]. Based on the Jacomy et al. study, the behavior of coronavirus-infected mice was reduced in a field test, all indicating depression and anxiety [38].

Rehabilitation points

Patients affected by neuromuscular injuries resulted from this disease need different rehabilitation measures based on their problem and injuries, in addition to routine treatment and medical care, which may vary from person to person. Rehabilitation of COVID-19 patients can improve pulmonary respiratory function; reduce physical complications such as bedsores, peripheral muscle weakness, muscle contractions, joint limitations, balance and postural disturbances, and physical weakness due to prolonged bed rest. It improves cognitive performance and enhances the quality of life. The issues related to these measures and the role and functional dimensions of COVID-19 patients’ rehabilitation are mentioned in a separate article published by some of the same authors [53].

2. Conclusion

The number of patients with COVID-19 is growing worldwide, while specific changes have been detected in the neuromuscular symptoms of this disease that have not been seen before. Therefore, neurologists should pay more attention to the possible signs of direct and indirect involvement of the nervous system and its lasting effects, which have been ignored in the acute phase of the disease.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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