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Neurological Complications of Corona Virus: A Mini-Review

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Abstract
Following the outbreak of COVID-19 disease, which is caused by the coronavirus, there were reports of neurological complications, indicating that virus infection may have risks involving the nervous system. Stroke, encephalopathy, moderate to severe headaches, anosmia and dysgeusia, hallucination, and depression were the most neurological complications reported. The most important neurological complication of COVID-19 is anosmia, which is caused by the infection of the olfactory support cells. Hallucination and depression have been observed in those admitted to the intensive care unit, which is primarily related to general inflammatory reactions. Although brain autopsies of people who have died because of COVID-19 have shown that the virus can be detected in brain tissue. Studies indicate that viral infection has only been detected in the vascular part of the blood-brain-barrier. Perhaps the most critical finding of coronavirus infection in the brain is the activation of astrocytes and microglia in patients with COVID-19, which dilates the cerebral arteries in the brainstem, allows killer T cells to enter brain tissue, and causes cytotoxic effects in this part of the brain. This review focused on the neurological complications associated with COVID-19 and the possible mechanisms underlying these complications.
Keywords: Anosmia; COVID-19; Depression; Dysgeusia; Hallucination; Headache; Stroke.

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Introduction

With the global outbreak of coronavirus and its disease (COVID-19), research and reports on how the virus affects the body and its complications have been considered by health organizations. Coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) enters cells in various areas of the body, including the lower lungs, by binding the S protein (Spike) to its receptor, which is the membrane-degrading enzyme angiotensin No. 2 (angiotensin-converting enzyme 2 -ACE2), mediated by cell surface transmembrane serine protease 2 (TMPRSS2), enters the cell and stimulates the transcription of its genetic material, leading to the death of host cells.[1] This suggests that if a cell did not express the ACE2 on its cell membrane, or that the membrane enzyme TMPRSS2 is not expressed in the cell membrane, the virus will not be able to enter the cell and the infection does not spread. On the other hand, it is clear that all viral disease related to the nervous system have host cells which express the virus receptors on their cell membrane. For example, poliovirus, which infects motor neurons in the spinal cord, can attach to these cells via its receptors and then destroys these neurons. Neuronal death is the main cause of paralysis of the motor part of the nervous system.[2,3] Also, the Japanese encephalitis, which is caused by the Japanese encephalitis virus, with 50 000 infections and 15 000 deaths per year is the result of direct infection of the neurons within the nervous system.[4] Since the outbreak of the COVID-19 pandemic, the question has been raised among the health professionals as to whether the coronavirus also enters the nervous system? And if so, what are the complications of virus entrance to the nervous system? And, next question was that how the professionals must deal with the situation? These questions arises because it was shown that another virus of these family namely the SARS virus could enter the nervous system. The novelty of COVID-19 disease and the lack of sufficient information on how the virus may enter the nervous system, raised a great deal of fear about the various complications of the virus, including the neurological complications caused by its entry into the nervous system. The discovery that the S1 virus protein is found in the cerebrospinal fluid (CSF) of mice infected with the coronavirus also increased the apprehensions.[5] In addition, reports indicated that symptoms such as loss of sense of smell and taste,[6] brain microvasculature bleeding[7] and stroke,[8] depression,[9] and hallucinations[10] were observed in people with COVID-19. However, the main question in this regard is whether the available evidence has shown a reason for the coronavirus to enter the nervous system? It is important to note that the coronavirus is known as a virus that attacks the lungs and destroys their cells, thereby reducing oxygen exchange capacity and lowering the blood oxygen saturation

percentage, leading to death.[11] For this reason, the need for histological and immunological studies of different areas of the brain in patients and victims of COVID-19 has become one of the main goals of research in the past year.[12] This review article provides a brief overview of medical articles in search engines such as PubMed, as well as important scientific sites such as *Nature* and Science and major medical journals including *the Lancet, New England Journal of Medicine*, and *JAMA* using keywords including nervous system, coronavirus, depression, headache, dizziness, hallucinations, brain, smell, taste, sight, hearing, touch, pain, spinal cord, CSF, cerebral cortex, to finally reach a conclusion about whether the virus can enter the nervous system and infect its cells or not.

How the Coronavirus Can Pass the Blood-Brain-Barrier and Enter the Brain

Studies on the possible entrance of the coronavirus into the brain has begun following the signs of neurological problems in patients suffering from COVID-19 disease.[13] Preliminary reports indicated a decrease in the level of consciousness of patients[10] and also, symptoms of depression[14] among patients. Then, a very important sign was seen in some reports that attracted a lot of attention. It was reported that some patients experience the loss of smell (anosmia), and taste (dysgeusia).[6] Because the olfactory receptors are the only part of the nervous system that is directly exposed to the external environment, it is very important to note that the virus may enter the nervous system via the olfactory receptors.[15] Subsequent reports of the appearance of fragments of the virus protein (S1) inside the mice olfactory bulb, which clearly indicated the virus entering the animal's nervous system,[5] reinforced speculation that in some patients the virus might be transmitted into the nervous system through the olfactory receptors and cause unknown neurological complications in individuals.[16] Other reports of stroke in patients suffered from COVID-19,[8] as well as reports in which indicated the existence of the virus in the autopsy of brain tissues of COVID-19 victims,[10] also raised concern for possible brain damage via a direct neuronal infection. For this reason, extensive efforts have been made over the past year to detect the virus entering the nervous system and its complications. The most important of these studies are in the field of virus entry into the nervous system through the olfactory system, the occurrence of complications such as depression and hallucinations in patients with COVID-19 and its causes, stroke in patients with COVID-19, and finally encephalopathy caused by COVID -19, which we will discuss below.

Coronavirus Enters the Brain Through the Olfactory Mucosa

Sensitivity to the possibility of coronavirus entering the nervous system stems from previous research suggesting that another member of the family, SARS-CoV, enters the nervous system of victims and causes neurological complications.[17] Because these viruses entered the nervous system through olfactory receptors located in the olfactory mucosa, the olfactory system and its function in patients suffering from COVID-19. Preliminary studies showed that in some patients with COVID-19, the olfaction is impaired, which indicates that the olfaction is affected. Based on these findings, the researchers suggested that coronavirus may enter the different parts of the brain via the olfactory tract and induce neurological complications.[18] This hypothesis, was enforced after the finding that the coronavirus virus S1 protein was found in the olfactory bulb of infected mice[5] and with the claim that the virus was observed in brain sections prepared from the autopsy of the victims of COVID-19.[19] However, new studies have shown that because of the lack of ACE2 on the cell membrane of the olfactory receptors, it seems that the chance of the coronavirus for entering the nervous system through the olfactory receptors is almost zero. Instead, olfactory support cells and stem cells, which play a protective role in supporting olfactory receptors, have large amounts of ACE2 i.e., the coronavirus receptors, and thus, can easily host the virus.[9] Various studies using MRI showed that there is a lot of dilation in the nasal mucosa of patients with the virus, which is due to infection of olfactory supporting cells. Because the supporting cells provide the crucial environment in terms of balanced water and electrolytes for the healthy functioning of olfactory cells, infection of these cells with coronavirus affects their normal functioning, which in turn changes the environment around olfactory receptors.[11] The changed environment possibly interferes with the normal function of the olfactory receptors and decreases or diminishes their function.[11] Another hypothesis for the loss of olfaction is the environmental inflammation in the olfactory mucosa following infection of the olfactory support cells. Studies have shown that following coronavirus infection, inflammatory cytokines are released from these cells and may affect the normal function of olfactory receptor neurons.[11] Finally, vascular rupture following inflammation may reduce blood flow and impair the proper functioning of olfactory receptors. It is worth noting that all these mechanisms may lead to the destruction of several olfactory receptors, resulting in disruption of olfaction.[11]

Hallucinations and Depression in Patients With COVID-19

Previous research has shown that patients with a variety of infectious diseases that affect the lungs also suffered from acute and/or chronic mental disorders.[19,20] Complications such as post-traumatic stress disorder, depression, insanity, and obsessive-compulsive disorder have also

been reported in patients with SARS and MERS for up to 50 months after infection.[21,22] Similar complications have also been reported in patients suffering from COVID-19. Researchers have reported that patients' afflicted withCOVID-19 also showed hallucinations, depression, and anxiety during and after recovery,[23] which even raised concerns about the huge wave of people with mental illness following COVID-19.[24] On the other hand, it should be noted that hallucinations are common in patients admitted to the intensive care unit, but the incidence of hallucinations is much higher in patients suffering from COVID-19 admitted to intensive care units.[11] Research about hallucinations in patients suffering from COVID-19 admitted to intensive care units is still ongoing, however, CSF examination of these patients indicates the presence of inflammatory cytokines, acidic proteins secreted by glial cells, and inflammatory proteins were present in this fluid.[20,25,26] In addition, researchers have suggested that very small hemorrhages (micro bleeding) in parts of the brain seen in MRI studies may cause complications, one of which is hallucinations.[8] What causes depression and anxiety in patients suffering from COVID-19? It is not yet known and only based on comparing the changes observed in patients with COVID-19 and mentally ill people, guesses could be made. The most important finding of changes in patients with COVID-19 is the occurrence of cytokine storm, which occurs following the coronavirus entrance which is the response of the immune system to the pathogen.[27] These cytokines can also cross the blood-brain-barrier and enter the nervous system. It has been shown that several neuronal dysfunctions following the entry of cytokines into the nervous system would occurred, which might lead to neurological problems ranging from mental illness to movement problems, and sensory dysfunction as well.[28] It is now believed that cytokines secreted by the immune system in response to infections and their penetration into the nervous system are involve in mental illness including depression and anxiety, in addition to the negative effects of psychological stress caused by the disease.[28] Investigators mentioned that lack of specific treatment and the danger of viral infection which may lead to the death can also complicate the situation of mental illness.[29] Interference between activities beyond the control of the immune system and problems related to psychological stress has been considered as the main basis for the occurrence of mental illnesses such as depression and anxiety in patients with COVID-19.[29] It must be noted that the complications are secondary to the main effect of the virus, and the reduction in arterial blood oxygen saturation percent due to reduced lung ventilation capacity add to the problem. For this reason, the use of drugs that reduce cytokine storms, such as corticosteroids, or the use of fluoxetine as an influencer of the brain's monoaminergic systems, might be useful and somewhat reduces the negative effects of COVID-19 on depression and anxiety.[20] In a nutshell; COVID-19 induces psychological symptoms such as depression, anxiety, and stress because of: (1) novelty of the disease, (2) fear of dying, (3) cytokine storm, and (4) dramatic drop in arterial oxygen saturation percent due to decreased lung ventilation capacity. Therefore, it seems that these complications are not due to direct infection of the brain by the virus.

Stroke in People With COVID-19

`Microvasculature bleeding and stroke are the most important complications reported in patients with COVID-19.[7,19] Although the percentage of patients with cerebral hemorrhage and stroke is not high (less than 1% of patients over 60 years admitted to the intensive care unit), this issue has been raised as a complication that should be considered by researchers.[1] It is hypothesized that the reason for stroke might be the decrease in cerebrovascular endothelial function due to cytokine storm.[8] However, there is no evidence of a direct effect of the virus on vascular endothelial cells, especially in the nervous system. Many researchers believe that COVID-19-induced stroke may occur in patients with a history of vascular disease. It is emphasized that in patients with COVID-19 who have a history of vascular disease such as hypertension, control of possible stroke must also be considered. Reducing the complications of stroke and the severity of involvement in different areas of the brain in patients with COVID-19 treated with corticosteroids indicate the existence of immune-dependent mechanisms in the occurrence of these strokes.[28] It is believed that stroke is a secondary complication of the virus infection and the cytokine storm induced by virus infection, and controlling the cytokine storm to some extent prevents its occurrence or at least reduces the prevalence of stroke in the brain.[28]

Presence of Coronavirus in the Brain Tissues

After the spread of COVID-19, and considering the fact that the coronavirus that causes it belongs to a family of viruses that has the ability to enter the nervous system,[17] researchers have considered whether the coronavirus is also able to enter the brain and infect the nerve cells? The virus is found in various parts of the nervous system and even inside the nerve cells.[28-30] But there is no explanation or indication of the presence of viral RNA inside the nerve cells or even astrocytes and other supporting cells using various immunohistochemical or PCR methods. Unlike other viruses in this family, which were able to enter the olfactory neurons and easily penetrate the nervous system, the coronavirus, which causes COVID-19, does not appear to penetrate in the nervous system. It should be noted that, as mentioned above, the cells of the nervous system did not express the receptors for the virus on their

membranes and also do not have the mechanism for the virus entrance after binding to ACE2. Taken together, one may resonate that opposite to the initial observations about the presence of the virus in the brain tissue sections of COVID-19 victims, it is clear that the observation of the virus in the brain tissues might be related to the weakness of studies and lack of efficient techniques for detecting the virus and its components in neurons.

COVID-19-Induced Encephalopathy

Encephalopathy due to COVID-19 has been added to the medical culture for less than a year. In studies of patients with COVID-19 with encephalopathy, high levels of inflammatory cytokines in plasma and CSF fluid have been reported.[25,26] Also, MRI studies of the brains of these patients has shown that the meninges of these patients are severely swollen and inflamed.[8] These findings are in line with the findings related to the inefficiency of cerebral vascular wall endothelial cells in these patients and indicate the effect of cytokine storm on the incidence of encephalopathy with cerebral hemorrhage and stroke in patients with COVID-19.[11] It should be noted that these findings are reported in a low percentage (less than 2%) of deaths due to COVID-19 and a high percentage of victims did not show these complications. Encephalopathy is especially evident in the brainstem and cerebellum, and patients with COVID-19 admitted to intensive care units have shown numerous symptoms of encephalopathy ranging from loss of consciousness to loss of movement or sensation in various parts of the body.[11] The cytokine storm that follows the coronavirus infection appears to play an important role in the development of COVID-19 induced encephalopathy.[27] In this regard, histological examination of the brains of COVID-19 victims has shown that in the brain blood vessels, especially in the brainstem, there is an increase in the permeability of the vessel wall and endothelial destruction.[10] On the other hand, microscopic hemorrhages in this area of the brain have been abundant.[10] Also, the abundance of astrocytes and microglia in this part of the brain can be a sign of extensive inflammation in this area following an increase in the permeability of the vascular wall of this part of the brain and the entry of high amounts of inflammatory cytokines to this part of the brain.[11] It seems that the presence of severe inflammation after the coronavirus infection on the one hand and the occurrence of multiple microscopic hemorrhages in the brainstem, on the other hand, is an important factor in the development and progression of encephalopathy due to COVID-19.

Conclusion

In this study, attempts were made to provide a more accurate picture of the current state of our knowledge about the neurological effects of coronavirus by reviewing the reports that have been published about the effect of COVID-19 on the incidence of diseases of the nervous system. According to the topics discussed in this study, it appears that the neurological complications of COVID-19 include those associated with cytokine storms, hypoxia due to decreased respiratory system ventilatory capacity, microscopic clots, or the ability of the virus to bind the endothelium of the brain vessels. These complications are due to infection of various cells in the nervous system, such as olfactory mucosal supporting cells or endothelial cells of the cerebral artery, and no direct effect of this virus on nervous system cells (neurons or other glial cells) has been reported. For this reason, treatments that prevent clots or inhibit cytokine storms and, of course, provide oxygen to vital tissues such as the brain, seem to increase the chances of reducing the neurological effects of COVID-19. At last, this study did not deal with peripheral nervous system and complications reported in this part of the nervous system such as Guillain-Barré syndrome. Moreover, the complications of autonomic nervous system were not mentioned in this study, which must be considered in the other studies.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Statement

Not applicable.

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