Coronavirus Disease 2019 (COVID-19) and Neurological Manifestations: A Potential Neuroinvasive Pathogen

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Abstract

Coronavirus disease 2019 (COVID-19) was first described in December 2019 in Wuhan, China, and rapidly widespread and became a global concern. In this outbreak, a new beta coronavirus from the order Nidovirales, which has a positive sense and single-stranded RNA genome, was identified. Herein, we would like to highlight the neurological complications of the COVID-19 and the neuroinvasive potential of this virus. It is worthy of mentioning that COVID-19 mainly causes acute respiratory distress syndrome, which is one of the most common causes of death. However, the latest studies demonstrated that, in severe cases, neurological manifestations can occur.

Keywords: Coronavirus, neuroinvasive, neurology, pandemic

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first described in December 2019 in Wuhan, China, and rapidly widespread and became a global concern. In this outbreak, a new beta coronavirus from the order Nidovirales, which has a positive sense and single-stranded RNA genome, was identified with a mortality rate of approximately 3%–4%.[1] The angiotensin-converting enzyme receptors are possibly responsible for the entry of this virus to the human cells, and these receptors are present on lung cells, renal tubular cells, arteries, gastric cells, and other tissues, including the central nervous system (CNS).[2] Figure 1 shows the importance of the COVID-19 to the public health-seeking behavior. It is noteworthy that for the first time since 2004, a disease was more popular than the most commonly searched words on Google (Facebook, YouTube, and Google) or a medicine topic (health).[3]

Herein, we would like to highlight the neurological complications of the COVID-19 and the neuroinvasive potential of this virus. It is worthy of mentioning that COVID-19 mainly causes acute respiratory distress syndrome, which is one of the most common causes of death. However, the latest studies demonstrated that, in severe cases, neurological manifestation can occur.
Summary of Recent Studies

It is already known that human coronaviruses can spread from the respiratory tract to the CNS through transneuronal and hematogenous routes.\(^4\) Even though these theories are feasible, other explanations for the neuronal damage could be direct damage to the lung tissue, leading to global hypoxia or an exacerbated inflammatory response [Figure 2].\(^2,5,6\) In this context, Mehta et al. observed that patients infected by COVID-19 may have a cytokine storm syndrome leading to multiorgan failure, which is characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony-stimulating factor, interferon-\(\gamma\) inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1-\(\alpha\), and tumor necrosis factor-\(\alpha\).\(^7,8\) Thus, they stated that “We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.”\(^7\)

The transneuronal route is by the invasion of the virus throughout the olfactory mucosa [Figure 3].\(^9,10\) One supporting finding of this hypothesis is the presence of anosmia in a high percentage of COVID-19 patients.\(^11\) Furthermore, studies with other types of coronavirus showed that about 30% of the anosmias is caused by a coronavirus.\(^12\) The majority of the individuals affected by COVID-19 only have mild symptoms, such as anosmia, cough, dyspnea, fever, headache, and myalgia, some develop acute respiratory distress syndrome after a week. Hence, one important question that arises is if this headache could be an earlier symptom of the occurrence of viral meningitis.

Another interesting point of discussion is the fact that some patients have developed encephalopathy. To be more specific, this is supported by three reports in the literature.\(^13-15\) The increasing number of individuals diagnosed with coronavirus worldwide would possibly turn the occurrence of rare clinical manifestations such as these more common. Therefore, physicians should be aware of these presentations among patients presenting with altered mental status and with or without respiratory symptoms.

A recent article by Mao et al. elucidated the nervous system complications observed in hospitalized patients with COVID-19. They classified these findings into skeletal muscular, CNS, and peripheral nervous system (PNS) symptoms. The CNS symptoms include dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy. The PNS were
hypogeusia, hyposmia, hypopsia, and neuralgia. The skeletal muscle system was only evaluated by the general-term muscle injury. Mao et al. found that patients with severe infection, when compared to those without a severe coronavirus infection, were more likely to have neurological manifestations (45.5% vs. 30.2%). From all those symptoms, only impaired consciousness, acute cerebrovascular disease, and muscle injury were statistically significant. Furthermore, the patients with severe CNS involvement when compared to those without a severe state demonstrated higher blood urea nitrogen levels, lower lymphocyte, and platelet counts. However, No laboratory findings were helpful for the prediction of PNS symptoms.[16]

It is worthy of mentioning that the majority of the patients with COVID-19 do not test positive for the virus in the cerebrospinal fluid (CSF). However, the report of the first patient with CSF positive for COVID-19 suggests considering direct neuroinfection when these individuals present with neurological symptoms. Furthermore, this report could partially explain why patients with a history of neurological illnesses are more susceptible to coronavirus infection.[17]

Immunocompromised patients are possibly particularly vulnerable to the infection by COVID-19. Other types of coronavirus have already been shown to be associated with severe neurological complications in this group of individuals.[18] Many neurological patients have autoimmune diseases (multiple sclerosis, myasthenia gravis, and neuromyelitis optica), and are on immunosuppressive therapies, which can cause systemic immune suppression and predispose them to severe infections.[19] In such patients is prudent to recheck dosages of the medications as well as reinforcing precautions. Furthermore, these drugs should not be withdrawn due to the risk of severe complications of underlying neurological diseases and the increased necessity of go to emergency centers and be more able to be infected by COVID-19. We believe that these last recommendations should also be followed by patients affected by headaches that are using Botox, and need to have their appointment, to avoid them go to the emergency department.[20]

Table 1 provides a summary of the information on neurological studies with COVID-19.[2,9,12-17,19,21-30]

**CONCLUSION**

In summary, we believe that awareness of physicians about neurological clinical manifestation could prompt the diagnosis and reduce the mortality rate in individuals infected with COVID-19. Future studies need to determine the risk factors and pathological explanations related to these neurological symptoms to help establishing specific management and reducing complications.

**Authors’ contribution**

Equal.

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Nil.

**Conflicts of interest**

None.

**Compliance with ethical principles**

Not applicable.
Table 1: Neurological symptoms and other important features already reported in association with severe acute respiratory syndrome-coronavirus 2

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COVID-19: Coronavirus disease 2019, CSF: Cerebrospinal fluid

REFERENCES

22. Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures


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