

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 spread widely 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.

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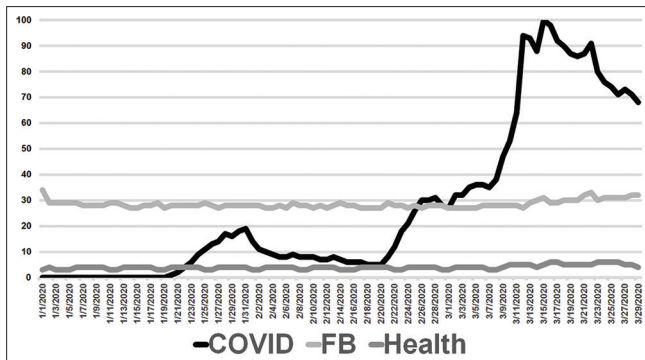


Figure 1: Google trends searching behavior of the terms “Coronavirus (COVID), Facebook (FB), and Health” from January to March 2020. To evaluate how often people search the Google to look for online information related to coronavirus disease, FB, and Health, we entered a set of keywords: “coronavirus,” “Facebook,” and “health” at the “Google Trends” main page, which was selected worldwide in the last 90 days (available at <https://trends.google.com/>, accessed on 03/31/2020). The number represents the search interest relative to the highest point on the chart for the given region and time, where higher values are associated with higher popularity of the term

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- γ inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1- α , and tumor necrosis factor- α .^[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

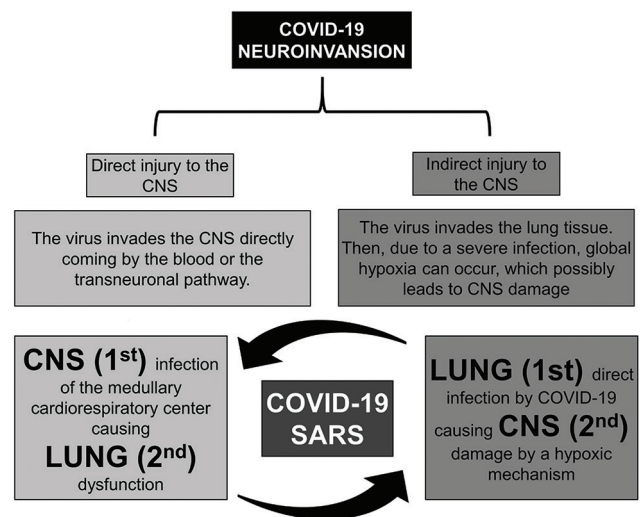


Figure 2: Pathogenesis of the central nervous system caused by coronavirus disease 2019. The indirect injury can be caused by a hypoxic mechanism or a systemic inflammatory response. SARS: severe acute respiratory syndrome

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

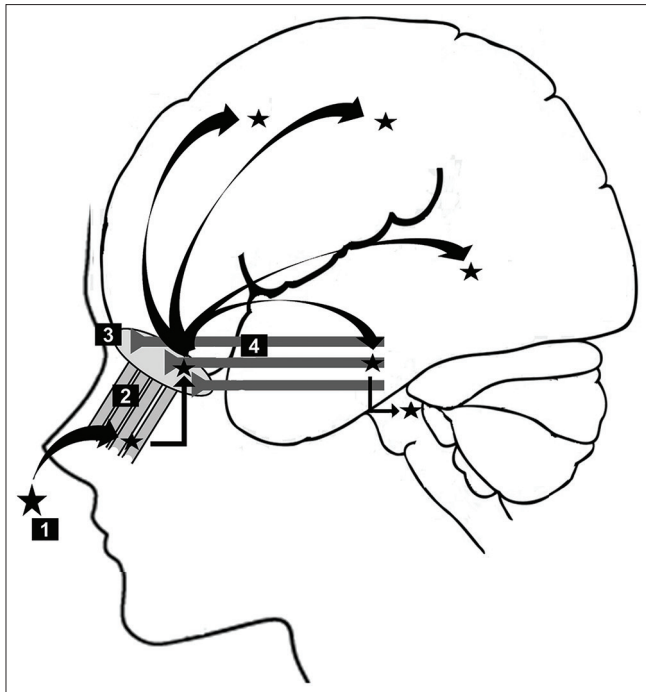


Figure 3: Schematic diagram of transneuronal invasion by HCoV-OC43, a coronavirus type. The virus (1, stars) invades the olfactory mucosa going by the olfactory sensory neurons (2) to the olfactory bulb (3). From the bulb, the virus invades the olfactory tract (4) which directly connects with the central nervous system

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

Reference	Description
Mao <i>et al.</i>	A retrospective study of the neurological manifestations in patients with COVID-19 Central nervous system symptoms: dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy Peripheral nervous system symptoms: hypogeusia, hyposmia, hypopsia, and neuralgia Skeletal muscle system symptoms: muscle injury
Wei <i>et al.</i>	Oculomotor nerve palsy
Filatov <i>et al.</i>	Encephalopathy
Li <i>et al.</i>	Coronaviruses neuroinvasion to the medullary cardiorespiratory center, a possible hypothesis to explain the lung and lower respiratory airways.
Hospital BD	The first patient with CSF positive for COVID-19, article in Chinese
Sun <i>et al.</i>	Clinical features of severe pediatric patients with COVID-19, one patient developed toxic encephalopathy
Iacobucci	Question and answers about the relation between anosmia and COVID-19
Hopkins and Kumar	Probably, the first description of the association between the loss of sense of smell as a marker of COVID-19 infection
Wu <i>et al.</i>	The five pathophysiological explanations of the coronavirus neuroinvasion: direct infection injury (blood circulation or neuronal pathway), hypoxia injury, angiotensin-converting enzyme 2, immune injury, and others (lack of major histocompatibility complex antigens in nerve cells)
Karimi <i>et al.</i>	A case report of reentrant generalized tonic-clonic seizures
Jacob <i>et al.</i>	Guidance for the management of myasthenia gravis and Lambert-Eaton myasthenic syndrome during the COVID-19
Clinicaltrials	Study assessing the efficacy of fingolimod in COVID-19 pneumonia
Poyiadji <i>et al.</i>	Acute hemorrhagic-necrotizing encephalopathy associated with COVID-19
National MS society	Guidance for the use of disease-modifying therapies in multiple sclerosis during the COVID-19 pandemic
Jiang <i>et al.</i>	Expert consensus on the management strategy of patients with hereditary ataxia, an article in Chinese
Brownlee <i>et al.</i>	Expert opinion of the United Kingdom about the management of multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic

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

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