Article published online: 2022-07-07

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

Jamir Pitton Rissardo[1], Ana Letícia Fornari Caprara[1]

[1]Department of Medicine, Federal University of Santa Maria, Santa Maria, Brazil

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.

Access this article online

Quick Response Code:

Website: www.ijmbs.org

DOI: 10.4103/ijmbs.ijmbs_37_20

Address for correspondence: Dr. Jamir Pitton Rissardo, Rua Roraima, Santa Maria, Rio Grande do Sul, Brazil. E-mail: jamirrissardo@gmail.com

Submitted: 04-Apr-2020 **Revised:** 04-Apr-2020
Accepted: 12-Apr-2020 **Published:** 27-Jun-2020

How to cite this article: Rissardo JP, Caprara AL. Coronavirus disease 2019 (COVID-19) and neurological manifestations: A potential neuroinvasive pathogen. Ibnosina J Med Biomed Sci 2020;12:85-9.

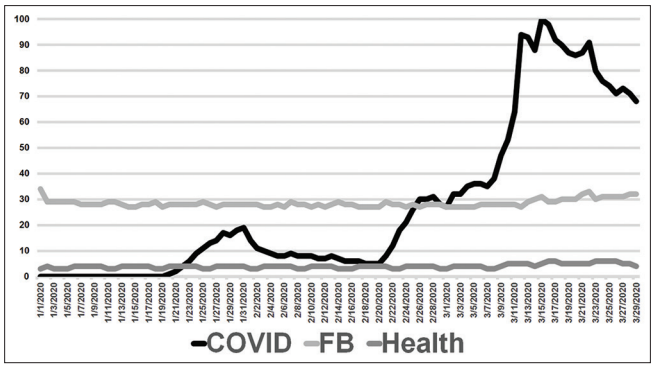

Figure 1: Google trends searching behavior of the terms "Coronavirus (COVID), Facebook (FB), and Health" from January to March 2020. To evaluate how often people search the Google to look for online information related to coronavirus disease, FB, and Health, we entered a set of keywords: "coronavirus," "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

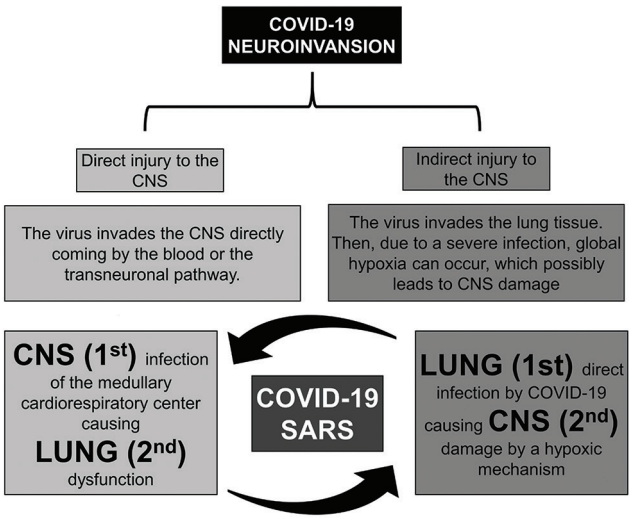

Figure 2: Pathogenesis of the central nervous system caused by coronavirus disease 2019. The indirect injury can be caused by a hypoxic mechanism or a systemic inflammatory response. SARS: severe acute respiratory syndrome

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 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

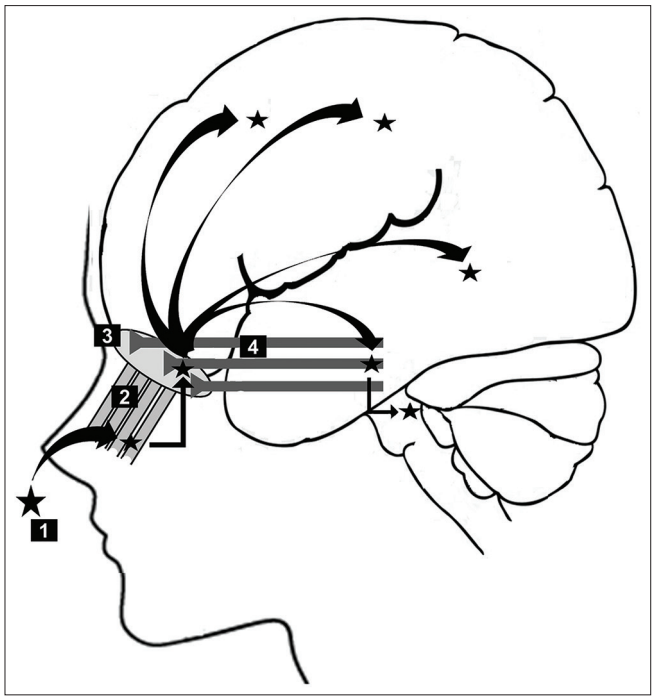

Figure 3: Schematic diagram of transneuronal invasion by HCoV-OC43, a coronavirus type. The virus (1, stars) invades the olfactory mucosa going by the olfactory sensory neurons (2) to the olfactory bulb (3). From the bulb, the virus invades the olfactory tract (4) which directly connects with the central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

Financial support and sponsorship

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 *et al*.	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 *et al*.	Oculomotor nerve palsy
Filatov *et al*.	Encephalopathy
Li *et al*.	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 *et al*.	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 *et al*.	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 *et al*.	A case report of reentrant generalized tonic-clonic seizures
Jacob *et al*.	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 *et al*.	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 *et al*.	Expert consensus on the management strategy of patients with hereditary ataxia, an article in Chinese
Brownlee *et al*.	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

References

1. Heo JY. Clinical and epidemiological characteristics of coronavirus disease 2019 in the early stage of outbreak. Korean J Med 2020;95:67-73.
2. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020 Mar 30:S0889-1591(20)30357-3. doi: 10.1016/j.bbi.2020.03.031. Epub ahead of print. PMID: 32240762; PMCID: PMC7146689.
3. Rissardo JP, Caprara AL. Parkinson's disease versus stroke versus seizure. Apollo Med 2020;17:50.
4. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci 2020;11:995-8.
5. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, *et al*. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – An update on the status. Mil Med Res 2020;7:11.
6. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by Coronavirus Disease 2019 and the corresponding immunotherapies. Zhonghua Shao Shang Za Zhi 2020;36:E005.
7. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al*. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
9. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, *et al*. Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? Viruses 2019;12:14.
10. Le Coupanec A, Desforges M, Meessen-Pinard M, Dubé M, Day R, Seidah NG, *et al*. Cleavage of a neuroinvasive human respiratory virus spike glycoprotein by proprotein convertases modulates neurovirulence and virus spread within the central nervous system. PLoS Pathog 2015;11:e1005261.
11. Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due to the 2019 Novel Coronavirus; a hypothesis that needs further investigation. Maxillofac Plast Reconstr Surg 2020;42:9.
12. Iacobucci G. Sixty seconds on. anosmia. BMJ 2020;368:m1202.
13. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy. Cureus. 2020 Mar 21;12(3):e7352. doi: 10.7759/cureus.7352. PMID: 32328364; PMCID: PMC7170017.
14. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, Liu ZS. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: A single center's observational study. World J Pediatr. 2020 Mar 19:1–9. doi: 10.1007/s12519-020-00354-4. Epub ahead of print. PMCID: PMC7091225.
15. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features [published online ahead of print, 2020 Mar 31]. Radiology. 2020;201187. doi:10.1148/radiol.2020201187
16. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, *et al*. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: A Retrospective Case Series Study; 2020.
17. Azhideh A. COVID-19 neurological manifestations. Int Clin Neurosci J 2020;2020:7.
18. Morfopoulou S, Brown JR, Davies EG, Anderson G, Virasami A, Qasim W, *et al*. Human coronavirus OC43 associated with fatal encephalitis. N Engl J Med 2016;375:497-8.
19. Nath A. Neurologic complications of coronavirus infections. Neurology 2020. pii: 10.1212/WNL.0000000000009455.
20. Stetka BS. What Neurologists Can Expect From COVID-19 2020. Available from: https://www.medscape.com/viewarticle/927562. [Last accessed on 2020 Apr 04].
21. Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. J Med Virol 2020.
22. Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures

in an adult patient with COVID-19: A case report. Iran Red Crescent Med J 2020;22:e102828.
23. Wei H, Yin H, Huang M, Guo Z. The 2019 novel cornoavirus pneumonia with onset of oculomotor nerve palsy: a case study. J Neurol. 2020 Feb 25:1–4. doi: 10.1007/s00415-020-09773-9. Epub ahead of print. PMCID: PMC7087661.
24. International MG/COVID-19 Working Group, Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, *et al*. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci 2020;412:116803.
25. Hopkins C, Kumar N. Loss of Sense of Smell as Marker of COVID-19 Infection. ENT UK; 2020.
26. Clinicaltrials. Fingolimod in COVID-19 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04280588. [Last accessed on 2020 Apr 04].
27. Hospital B. Clinicians and Researchers have Confirmed for the First time That SARSCoV-2 Can Cause Central Nervous System Infection; 2020. Available from: http://www.bjdth.com/html/1/305/307/index.html?messageId=3665. [Last accessed on 2020 Apr 04].
28. Society NM. Disease Modifying Treatment Guidelines for Coronavirus (COVID-19); 2020. Available from: https://www.nationalmssociety.org/What-you-need-to-know-about-Coronavirus-(COVID-19)/DMT-Guidelines-for-Coronavirus-(COVID-19)-and. [Last accessed on 2020 Apr 04].
29. Specialized Committee of Neurogenetics Neurophysician Branch of Chinese Medical Doctor Association, Jiang H, Tang B. Expert consensus on the management strategy of patients with hereditary ataxia during prevention and control of novel coronavirus pneumonia epidemic. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2020;37:359-66.
30. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. Neurology 2020. pii: 10.1212/WNL.0000000000009507.