Journal of
Pharmacology & Clinical Research
ISSN: 2473-5574

Juniper Publishers
key to the Researchers

Review Article
Volume 10 Issue 1 - March 2024
DOI: 10.19080/JPCR.2024.10.555780

J of Pharmacol & Clin Res


# The Neuro-Invasive Potential of SARS-CoV-2 and Possible Neurological Complications

**Justin T. Crawmer[1], Lei Zhao[2], Austin J Marrah[3], Trenton G Mayberry[3], Braydon C Cowan[3], Mena M Saad[1] , Qian Bai[3], Mark R Wakefield[3] and Yujiang Fang[1,3]***

[1]*Department of Microbiology, Immunology & Pathology, Des Moines University, Des Moines, IA, USA*

[2]*The Department of Respiratory Medicine, the 2nd People's Hospital of Hefei and Hefei Hospital Affiliated to Anhui Medical University, Hefei, China*

[3]*The Department of Surgery, University of Missouri School of Medicine, Columbia, MO, USA*

**Submission:** February 14, 2024; **Published:** March 21, 2024

***Corresponding author:** Yujiang Fang, Department of Microbiology, Immunology & Pathology, Des Moines University College of Osteopathic Medicine, Des Moines, Iowa, USA

**Abstract**

The current global pandemic caused by SARS-Cov-2 is a heavily researched topic. Labs are throwing endless time and money into understanding, fighting the spread, and reducing the damage caused by SARS-CoV-2. COVID-19 has many known symptoms that distinguish the specific tissues the virus affects, yet there are still so many unknowns on its overall effect on the body. Our lab is interested in understanding the possible short-term and long-term damage the virus causes to the brain. Looking into how SARS-CoV-2 enters and attacks tissues in the body is crucial in unraveling possible damage to the brain. Some studies on the pathogenesis of COVID-19 provided insight into the ability of the virus to infect the brain. The significant neurotrophic potential of SARS-CoV-2 warrants studies aiming to reduce or even prevent brain damage and other complications. This review gathers recent studies investigating manifestations and complications of COVID-19 on the brain and other neurological systems. Further, this review might be helpful for future studies on the pathogenesis of SARS-CoV-2 on the brain and other neurological systems.

**Keywords:** Brain; COVID-19; SARS-CoV-2; Neurological Manifestations; Central Nervous System; Angiotensin-Converting Enzyme 2 Receptor; Long-COVID

**Abbreviations:** SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; CNS: Central Nervous System; ACE2: Angiotensin-Converting Enzyme 2; BBB: Blood-brain-barrier; SIC: Sepsis-induced Coagulopathy

## Introduction

In late December 2019, patients in Wuhan, China, emerged with pneumonia-like symptoms due to an unknown pathogen. These symptoms were linked to a seafood and wet animal wholesale market [1]. The unknown pathogen is now known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 has spread exponentially worldwide through human-to-human transmission, causing global attention. Due to the infectious ability of SARS-CoV-2, countries have taken precautions, including vaccinations, to combat the spread of the virus. Despite these added precautions, the viral pandemic has infected 774,469,939 individuals and has caused 7,026,465 deaths worldwide as of January 28th, 2024 [2]. The clinical presentation of COVID-19 continues to vary widely. SARS-CoV-2 infection can manifest with symptoms from many body systems including, but not limited to, the pulmonary system, cardiovascular system, gastrointestinal system, and even the neurological system.

## Clinical Presentations of COVID-19

Common minor symptoms experienced by individuals infected by SARS-CoV-2 include cough, fever, chills, fatigue, sore throat, anosmia, ageusia, and many more. Some patients with COVID-19 present more severe symptoms, which may lead to acute respiratory distress syndrome. Moreover, severely affected patients are more likely to develop neurological symptoms compared to patients who have mild to moderate cases [3]. Evidence has shown that SARS-CoV-2 can infect the central nervous system (CNS), causing neurological damage and warranting concern for the potential permanent or long-term

damage of SARS-CoV-2. The full extent of SARS-CoV-2 has yet to be thoroughly investigated. New studies are bringing to light the multiorgan effects of SARS-CoV-2, and further studies shall aim to understand the potential mechanisms of neural injury.

## Possible Pathogenesis of CNS Damage by SARS-CoV-2

Previous studies found that SARS-CoV-2 can infect tissues by interacting with the angiotensin-converting enzyme 2 (ACE2) receptor, a highly expressed receptor in epithelial tissues and many other major organs [4]. A higher density of ACE2 receptors in various tissues is thought to result in a higher severity of infection by SARS-CoV-2 [5-7]. Patients with a smoking history tend to have more negative outcomes and more rapid disease progression of COVID-19. It is necessary to emphasize that higher levels of ACE2 receptors have been observed in the brains of smokers [8]. With those observations in mind, it is possible that smoking increases the ability of SARS-CoV-2 to infect the brain due to higher densities of ACE2 receptors [9]. Early clinical presentations of ageusia and anosmia in COVID-19 patients indicate the ability of SARS-CoV-2 to infect the brain as well as other parts of the CNS. Ageusia and anosmia indicate the ability of SARS-CoV-2 to infect the olfactory and gustatory pathways [10-12]. With anosmia hinting at the possible early invasive potential of SARS-CoV-2 through the olfactory bulb to the olfactory nerve and CNS [13].

Two major routes proposed for SARS-CoV-2 infection into the brain are the hematogenous and neuronal retrograde routes [14-17]. In the hematogenous route, the virus infects the epithelial cells of the blood-cerebrospinal fluid barrier and/or the endothelial cells of the blood-brain-barrier (BBB) in its path to invading the brain [18]. Postmortem examination of the brains of COVID-19 patients who presented with neurological changes upon infection has further supported this route of invasion. Upon examination, viral particles were found by electron microscopy in frontal lobe neurons and endothelial cells of capillaries in the brain, both unveiling direct evidence of SARS-CoV-2 in human brain tissue [19]. Besides the hematogenous pathway, another source of infection is through the neuronal retrograde route. The neuronal retrograde route of invasion proposes that the virus invades the CNS by infecting peripheral neurons; this is further supported by the common symptoms of ageusia and anosmia. Both the hematogenous and neuronal retrograde routes support significant neurotropic potential, warranting studies aiming to further understand the pathways in which the virus invades the CNS and brain.

Once in the CNS, SARS-CoV-2 can invade and damage brain cells, principally the astrocytes [19]. Astrocytes are brain cells essential for the maintenance of brain homeostasis and contribute to the secretion of inflammatory mediators and other neurotropic mediators including GFAP and NfL [20-22]. A recent study suggests that severe COVID-19 infection is correlated with increased concentrations of GFAP and NfL, which are both important molecules in the brain and are now regarded as biomarkers for neural injury [23]. This supports the idea that astrocyte activation may be a characteristic feature indicating brain damage caused by SARS-CoV-2 in severe infection. A more recent study by Lee et al. [24], which aimed at studying the neuropathological changes in postmortem brain tissue using immunohistochemistry found that the most likely mechanism of injury to endothelial cells is antibody-mediated cytotoxicity caused by SARS-CoV-2 [24]. The researchers also found immune complex deposition and activation of the complement pathway on endothelial cells and platelets [24]. It is also important to note that of these patients who died from severe COVID-19 infection, some had minimal lung involvement at the time of their death [24].

## Other Neurological Presentations Related to COVID-19

Besides the above-mentioned ageusia and anosmia, there are other neurological complications observed from COVID-19, particularly in severe cases of COVID-19 due to rapid dissemination to the brain tissues in patients. Studies have started to investigate neurological complications of COVID-19 and examine possible treatments to prevent complications. Stroke is emerging as a complication of the COVID-19 pandemic [25]. Although the cause of COVID-19-related stroke is unknown, sepsis-induced coagulopathy (SIC) is associated with COVID-19 due to high D-dimer levels and elevated fibrinogen [26,27]. Due to the SARS-CoV-2 infection-induced inflammatory response, it is thought that stroke may be due to the dysfunction of endothelial cells [25]. Another complication observed in COVID-19 patients is cerebral edema caused by hypoxic brain injury [28,29].

Furthermore, case studies have unveiled a clear link between severe SARS-CoV-2 infection and neurological manifestations such as encephalitis, seizures, and stroke [18]. SARS-CoV-2 can also cause brain damage due to inflammation of the brain parenchyma (encephalitis) from the body's response to viral infection [30]. The incidence of neurological complications is still unknown, and the virus should be further studied to develop treatments combating long-term damage. Proper treatment and prevention could result in a decrease in mortality rates for COVID-19, especially for the elderly and other at-risk patients. Although the above-mentioned effects of COVID-19 on the CNS are well documented, it is also important to note that in a study examining neuronal tissue in postmortem patients who had severe COVID-19 infection, SARS-CoV-2 was not detected in their brain tissue [31]. This further solidifies that the inflammatory response is the main reason for neuronal injury rather than the direct effects of SARS-CoV-2 on brain tissue.

## Possible Treatments for Neuronal Injury Caused by Acute COVID-19

The treatment of COVID-19 is an ever-evolving topic. Since the beginning of the pandemic, many different therapeutics have been introduced and utilized to treat the virus. Ivermectin, a cheap and relatively available drug with anti-fungal, anti-viral,


How to cite this article: Justin T. C, Lei Z, Austin J M, Trenton G M, Braydon C C, et al. The Neuro-Invasive Potential of SARS-CoV-2 and Possible Neurological Complications. J of Pharmacol & Clin Res. 2024; 10(1): 555780. DOI: 10.19080/JPCR.2024.09.555780

and anti-inflammatory properties was introduced as a possible treatment for COVID-19 [32]. A study by Reis et al. [33] debunked its therapeutic efficacy by showing that Ivermectin did not significantly decrease disease progression [33]. Other treatments, including intravenous and oral steroids, have been commonly used to decrease inflammation in various disease states. A randomized control trial by Horby et al. [34] documented the benefits of using low-dose dexamethasone to reduce the 28-day mortality of patients with severe COVID-19 infection [34]. Though this finding was promising in reducing the inflammatory damage of lung tissue, low-dose dexamethasone is not able to reach therapeutic levels to treat inflammation of the CNS.

A study by Cardenas et al. [35] is currently investigating the therapeutic benefit of intranasal dexamethasone for the treatment of neuroinflammation caused by the virus [35]. If proven to be beneficial in reducing mortality, this may be an excellent treatment option because it allows low doses of corticosteroids to be beneficial and prevents the potential side effects of using high-dose systemic steroids to combat neuroinflammation [35]. Targeted compounds specifically aimed at reducing the neuronal inflammation caused by SARS-CoV-2 are a hot topic of clinical research. In a recent study by Gudson et al. [36], a dendrimer nano-compound termed "OP-101" was shown to reduce neuronal injury markers such as neurofilament light chain and glial fibrillary acidic protein [36]. Although the study is still in the clinical phase 2a trial, the composite outcome for mechanical ventilation or death at 30 and 60 days was 71% (95% CI: 29%, 96%) for the group receiving traditional therapies and 18% (95% CI: 4%, 43%; P = 0.021) for the OP-101 treated group [36].

### The "Long-COVID" Syndrome

The acute effects of COVID-19 on mortality and morbidity have been the center of research topics since the beginning of the pandemic. Although definitions and criteria differ between the different organizations, the WHO defines post-COVID syndrome, also called "Long-COVID syndrome" as symptoms including fatigue, shortness of breath, and cognitive dysfunction that arise within 3 months of the onset of COVID-19 and last for at least 2 months and cannot be explained by an alternative diagnosis [37]. As the focus has been on understanding new emerging variants of SARS-CoV-2, studies investigating the sequelae of acute COVID-19 infection have shown that as many as 61% of patients had persistent symptoms at the 6-month mark [38]. One study noted that 13% and 11% of patients were experiencing lasting impaired concentration and memory problems, respectively [38]. Further studies investigating the mental health implications of these lasting effects would be beneficial. Treatments aimed at reducing the effects of post-Covid syndrome have also been promising. Oxaloacetate has been shown to decrease the physical and mental fatigue caused by post-COVID syndrome, with one study boasting a 46.8% reduction in fatigue at the 6-week mark [39]. A study by De Luca et al. [40] investigated the benefits of palmitoylethanolamide and luteolin on the relief of mental clouding and the return of olfactory senses. Their study showed an improvement in both olfaction and memory, providing a possible treatment option to combat the "brain fog" that many patients suffer from after recovering from acute COVID-19 infection [40].

## Conclusion

The neuroinvasive potential of SARS-CoV-2 has yet to be appropriately investigated, but current studies have identified CNS involvement and neurological manifestations of COVID-19 as important aspects in understanding its widespread presentations. Understanding the neuroinvasion of SARS-CoV-2 may reveal why only some patients develop respiratory failure. Further studies shall investigate the mechanisms SARS-CoV-2 used to infect the CNS with an aim to develop treatments to decrease the effect of neurological manifestations, especially for patients severely affected by COVID-19. Furthermore, studies should investigate patients who experience complications such as stroke or cerebral edema to develop treatments and better understand the pandemic virus. Investigating the "Long-COVID" syndrome can provide further information to help combat the effect of the virus. Even though the prevalence of neurological complications is low, the scale of the current pandemic means even a small proportion can add to significant cases. Currently, this is the major research on the neurotropic potential of COVID-19. Despite the success of the vaccines for SARS-CoV-2, there is still an extreme need to better understand the pathogenesis of SARS-CoV-2, as well as develop treatments to decrease the neurological manifestations and complications experienced by severely infected individuals.

## Acknowledgment

Yujiang Fang and Lei Zhao initiated the idea. Justin T. Crawmer, Lei Zhao, Austin J. Marrah, Trenton G. Mayberry, Braydon C. Cowan, Mena M. Saad, and Qian Bai wrote the draft. Yujiang Fang and Wakefield made critical revision to the draft. This study was partially supported by a grant for Dr.Yujiang Fang: IOER 112-3749.

## References

1. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, et al. (2020) Pneumonia of unknown etiology in Wuhan, China: potential for international spread via commercial air travel. J Travel Med 27(2): taaa008.
2. World Health Organization 2(023) WHO Coronavirus (COVID-19) dashboard > Cases [Dashboard].
3. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 77(6): 683-690.
4. Letko M, Marzi A, Munster V (2020) Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 5(4): 562-569.
5. Xu H, Zhong L, Deng J, Peng J, Dan H, et al. (2020) High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 12(1): 8.


How to cite this article: Justin T. C, Lei Z, Austin J M, Trenton G M, Braydon C C, et al. The Neuro-Invasive Potential of SARS-CoV-2 and Possible Neurological Complications. J of Pharmacol & Clin Res. 2024; 10(1): 555780. DOI: 10.19080/JPCR.2024.09.555780

6. Jia HP, Look DC, Shi L, Hickey M, Pewe L, et al. (2005) ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol 79(23):14614-14621.

7. Gallagher TM, Buchmeier MJ (2001) Coronavirus spike proteins in viral entry and pathogenesis. Virology 279(2): 371-374.

8. Liu W, Tao ZW, Wang L, Yuan M, Liu K, et al. (2020) Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 133(9): 1032-1038.

9. Choi JY, Lee HK, Park JH, Cho S, Kwon M, et al. (2020) Altered COVID-19 receptor ACE2 expression in a higher risk group for cerebrovascular disease and ischemic stroke. Biochem Biophys Res Commun 528(3): 413-419.

10. Chiesa-Estomba CM, Larruscain-Sarasola E, Lechien JR, Mouawad F, Calvo-Henriquez C, et al. (2021) Facial nerve monitoring during parotid gland surgery: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol 278: 933-943.

11. Gervasoni C, Meraviglia P, Riva A, Giacomelli A, Oreni L, et al. (2020) Clinical features and outcomes of HIV patients with coronavirus disease 2019. Clin Infect Dis 71(16): 2276-2278.

12. Hannum ME, Ramirez VA, Lipson SJ, Herriman R, Toskala A, et al. (2020) Objective Sensory Testing Methods Reveal a Higher Prevalence of Olfactory Loss in COVID-19-Positive Patients Compared to Subjective Methods: A Systematic Review and Meta-Analysis. Chem Senses 45(9): 865-874.

13. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, et al. (2020) Neurological Involvement in COVID-19 and Potential Mechanisms: A Review. Neurocrit Care 34(3): 1062-1071.

14. Baig AM (2020) Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther 26(5): 499-501.

15. Baig AM, Khaleeq A, Ali U, Syeda H (2020) Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci 11(7): 995-998.

16. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, et al. (2020) Endothelial cell infection and endotheliitis in COVID-19. Lancet 395(10234): 1417-1418.

17. Zhou Z, Kang H, Li S, Zhao X (2020) Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol 267(8): 2179-2184.

18. Rodriguez M, Soler Y, Perry M, Reynolds JL, El-Hage N (2020) Impact of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in the Nervous System: Implications of COVID-19 in Neurodegeneration. Front Neurol 11: 583459.

19. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon R, Reidy J, et al. (2020) Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 92(7): 699-702.

20. Farina C, Aloisi F, Meinl E (2007) Astrocytes are active players in cerebral innate immunity. Trends Immunol 28(3): 138-145.

21. Soung A, Klein RS (2018) Viral Encephalitis and Neurologic Diseases: Focus on Astrocytes. Trends Mol Med 24(11): 950-962.

22. Verkhratsky A, Parpura V, Vardjan N, Zorec R (2019) Physiology of Astroglia. Adv Exp Med Biol 1175: 45-91.

23. Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, et al. (2020) Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology 95(12): e1754-e1759.

24. Lee MH, Perl DP, Steiner J, Pasternack N, Li W, et al. (2022) Neurovascular injury with complement activation and inflammation in COVID-19. Brain 145(7): 2555-2568.

25. Hess DC, Eldahshan W, Rutkowski E (2020) COVID-19-Related Stroke. Transl Stroke Res 11(3): 322-325.

26. Iba T, Levy JH, Warkentin TE, Thachil J, Van der Poll T, et al. (2019) Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost 17(11): 1989-1994.

27. Tang N, Bai H, Chen X, Gong J, Li D, et al. (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18(5): 1094-1099.

28. Xu Z, Shi L, Wang Y, Zjang J, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8(4): 420-422.

29. Ahmad I, Rathore FA (2020) Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci 77: 8-12.

30. Ellul MA, Benjamin L, Singh B, Lant S, Michael B, et al. (2020) Neurological associations of COVID-19. Lancet Neurol 19(9): 767-783.

31. Lee MH, Perl DP, Nair G, Li W, Maric D, et al. (2021) Microvascular Injury in the Brains of Patients with Covid-19. N Engl J Med 384(5): 481-483.

32. Bryant A, Lawrie T, Dowswell T, Fordham E, Mitchell S, et al. (2021) Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. Am J Ther 28(4): e434-e460.

33. Reis G, Silva E, Silva D, Thabane L, Milagres A, et al. (2022) Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med 386(18): 1721-1731.

34. Horby P, Lim W, Emberson J, Mafham M, Bell J, et al. (2021) Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 384(8): 693-704.

35. Cárdenas G, Chávez-Canales M, Espinosa A, Jordán-Ríos A, Malagon D, et al. (2022) Intranasal dexamethasone: a new clinical trial for the control of inflammation and neuroinflammation in COVID-19 patients. Trials 23(1): 148.

36. Gusdon A, Faraday N, Aita J, Kumar S, Mehta I, et al. (2022) Dendrimer nanotherapy for severe COVID-19 attenuates inflammation and neurological injury markers and improves outcomes in a phase2a clinical trial. Sci Transl Med 14(654): eabo2652.

37. Soriano J, Murthy S, Marshall J, Relan P, Diaz J (2022) A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis (4): e102-e107.

38. Blomberg B, Mohn K, Brokstad K, Zhou F, Linchausen D, et al. (2021) Long COVID in a prospective cohort of home-isolated patients. Nat Med 27(9): 1607-1613.

39. Cash A, Kaufman DL (2022) Oxaloacetate Treatment For Mental And Physical Fatigue In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long-COVID fatigue patients: a non-randomized controlled clinical trial. J Transl Med 20(1): 295.

40. De Luca P, Camaioni A, Marra P, Salzano G, Carriere G, et al. (2022) Effect of Ultra-Micronized Palmitoylethanolamide and Luteolin on Olfaction and Memory in Patients with Long COVID: Results of a Longitudinal Study. Cells 11(16): 2552.



How to cite this article: Justin T. C, Lei Z, Austin J M, Trenton G M, Braydon C C, et al. The Neuro-Invasive Potential of SARS-CoV-2 and Possible Neurological Complications. J of Pharmacol & Clin Res. 2024; 10(1): 555780. DOI: 10.19080/JPCR.2024.09.555780

DOI: 10.19080/JPCR.2024.09.555780




**How to cite this article:** Justin T. C, Lei Z, Austin J M, Trenton G M, Braydon C C, et al. The Neuro-Invasive Potential of SARS-CoV-2 and Possible Neurological Complications. J of Pharmacol & Clin Res. 2024; 10(1): 555780. DOI: 10.19080/JPCR.2024.09.555780