Received: 6 April 2020 | Accepted: 21 April 2020

DOI: 10.1002/jmv.25918

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

The emergence of a novel coronavirus (SARS-CoV-2) disease and their neuroinvasive propensity may affect in COVID-19 patients

H.C. Yashavantha Rao PhD | Chelliah Jayabaskaran PhD

Department of Biochemistry, Indian Institute of Science, Bengaluru, Karnataka, India

Correspondence
H.C. Yashavantha Rao, PhD, Department of Biochemistry, Indian Institute of Science, Bengaluru, Karnataka 560 012, India.
Email: hcyrao@gmail.com

Abstract

An outbreak of a novel coronavirus (SARS-CoV-2) infection has recently emerged and rapidly spreading in humans causing a significant threat to international health and the economy. Rapid assessment and warning are crucial for an outbreak analysis in response to serious public health. SARS-CoV-2 shares highly homological sequences with SARS-CoVs causing highly lethal pneumonia with respiratory distress and clinical symptoms similar to those reported for SARS-CoV and MERS-CoV infections. Notably, some COVID-19 patients also expressed neurologic signs like nausea, headache, and vomiting. Several studies have reported that coronaviruses are not only causing respiratory illness but also invade the central nervous system through a synapse-connected route. SARS-CoV infections are reported in both patients and experimental animals' brains. Interestingly, some COVID-19 patients have shown the presence of SARS-CoV-2 virus in their cerebrospinal fluid. Considering the similarities between SARS-CoV and SARS-CoV-2 in various aspects, it remains to clarify whether the potent invasion of SARS-CoV-2 may affect in COVID-19 patients. All these indicate that more detailed criteria are needed for the treatment and the prevention of SARS-CoV-2 infected patients. In the absence of potential interventions for COVID-19, there is an urgent need for an alternative strategy to control the spread of this disease.

KEYWORDS

central nervous system, coronavirus, COVID-19, MERS, neuroinvasive, SARS

1 | INTRODUCTION

It is surprising that the 2020 year started with the report of a dreaded novel viral coronavirus (SARS-CoV-2) disease threat in China and spreading all over the globe. World Health Organization (WHO) has declared coronavirus disease-2019 (COVID-19) a Public Health Emergency of International Concern. Various changes in environmental factors and human behaviors have led towards the emergence of more than 30 new infectious diseases in the last 3 decades, ranging from rotavirus to Middle East respiratory syndrome coronavirus.[1] The increasing human population, people movement across diverse borders, rapid expansion of air traffic, changes in the climate have modified the ecosystem has made these novel pathogens can easily spread across the world.

2 | COVID-19

On 31st December 2019, Chinese health authorities investigated a cluster of atypical cases of pneumonia mainly occurring in individuals who visited Huanan seafood wholesale Market in Wuhan, Hubei Province, China. From 31st December 2019 to

3rd January 2020, a total of 44 patients developed symptoms like cough, fever, and chest discomfort or respiratory illness, being diagnosis of pneumonia constituted by chest radiographs and computed tomographic scans.[2] During this period, the causal agent was not known. After testing for the causes of respiratory infection encode the negative result, an unbiased sequence of bronchoalveolar lavage fluid identified a β-coronavirus variant with sequences similarity of 85% corresponding to a bat severe acute respiratory syndrome (SARS) like coronavirus (CoV).[2] Later, the virus was isolated in eukaryotic cells culture, and further identification indicated that it was distinct from SARS-CoV (sequence homology 79%) and the Middle East respiratory syndrome (MERS)-CoV (sequence homology 50%).[3] The sequences were deposited in GenBank (accession number MN908947). The International Committee on Taxonomy of Viruses named this CoV variant as SARS-CoV-2,[4] representing the 7th CoV to cause disease in human beings, and 3rd CoV since 2003 to spread from animals to humans related with respiratory illness.[2] WHO has named this respiratory illness as coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2.

As of 19th April 2020, the COVID-19 outbreak had resulted in nearly 2.24 million laboratory-confirmed cases, including 1.52 lakhs death all around the world.[5] Currently, no suitable vaccines or antiviral drugs are available for SARS-CoV-2. Early warning is very crucial measures to control the outbreak and epidemics of infectious diseases. Rapid and reliable diagnostic methods for the detection of SARS-CoV-2 is crucial for public health interventions that can minimize the spread of COVID-19.

3 | THE CLINICAL FEATURES OF COVID-19

SARS-CoV-2 causes pneumonia with clinical symptoms of SARS-CoV and MERS-CoV infections.[6,7] Clinical features of SARS-CoV-2 infection showed non-productive cough, dyspnea, myalgia, fever, normal or decreased leukocyte counts, fatigue, and pneumonia. Organ dysfunctions like shock, acute cardiac injury, acute kidney injury, acute respiratory distress syndrome (ARDS), and death occurs in severe cases. Most of these clinical features of patients had a history of exposure to Huanan seafood whole-sale market. Later on, Chen et al[8] documented his findings from 99 pneumonia cases indicated that the 2019-nCoV infection clustered within the group of human close contact and likely to affect older men with comorbidities and results in ARDS. About 46% to 65% of the patients in the intensive care worsened in a short period and died due to respiratory failure.[8,9]

It is not clear that CoVs are continuously confined to respiratory illness, indeed they additionally invade the central nervous system (CNS) with neurological diseases. Such neuroinvasive tendency of CoVs has been reported in all β-CoVs, including HCoV-229E,[10] SARS-CoV,[11] MERS-CoV,[12] HCoV-OC43,[13] and porcine hemagglutinating encephalomyelitis CoV.[14-16] The high resemblance between SARS-CoV and SARS-CoV-2 remains to explore whether the potent neuroinvasion of SARS-CoV-2 plays a significant role in COVID-19 infections.

4 | THE NEUROINVASIVE PROPENSITY OF SARS-CoV-2

SARS-CoV entry into the human host cell is mediated primarily by cellular receptors angiotensin enzyme-2 (ACE2) that is expressed in the lung parenchyma, kidney cells, vascular endothelia, small intestine cells, and human airway epithelia.[17-19] MERS-CoV enters humans host cells primarily by dipeptidyl peptidase-4 (DPP4) in the cells of the immune system, liver, small intestine, and lower respiratory tract.[20,21] Indeed, ACE2 or DPP4 alone is not enough to make the host cell susceptible to infections. SARS-CoV or MERS-CoV infections were also reported in the CNS, where ACE2 or DDP4 expression level is low under normal conditions.[22] The accurate route where SARS-CoV and MERS-COV enter CNS is still not clearly documented. Indeed, the lymphatic or hematogenous path seems to be impossible, particularly in the initial infection stage and there were no virus particles were detected in the infected brain area.[23-25] However, several shreds of evidence indicate that CoVs may initially invade peripheral nerve terminal, and later to the CNS through a synapse-connected route.[14,16,26,27] The trans-synaptic transfer has been reported for HEV67 CoV,[9,15,16] and avian bronchitis virus.[27,28]

Earlier studies on SARS patient samples have shown the presence of SARS-CoV particles in the brain and located exclusively in the neurons.[23,25] In-vivo experiments using transgenic mice showed that, when SARS-CoV or MERS-COV has given intranasally, it can enter the brain via the olfactory nerve, and quickly spreads to certain specific brain regions like brainstem and thalamus.[29,30] Among the infected brain areas, the brainstem has been heavily infected by SARS-CoV or MERS-CoV.[29-31] The brain has expressed ACE2 receptors that have been detected over neurons and glial cells which makes them a potential target of COVID-19. Another important observation was those mice infected with MERS-CoV with less inoculum doses, virus particles were not detected in the lung, but only in the brain, which indicates that the CNS infection was more important for the high mortality.[30]

Porcine hemagglutinating encephalomyelitis virus (PHEV; family Coronaviridae; genus Coronavirus) causes vomiting and encephalomyelitis disease in suckling piglets.[32,33] Earlier studies have shown that the virus is propagated through the neural route and has a potent tropism in the upper respiratory tract.[34] HEV 67N CoV is the first coronavirus that showed to invade the porcine brain.[30,35] HEV 67N-infected mice group exhibited typical neurological damage with symptoms of depression, standing/vellicating front claws, and arched waists after 3 days of postinoculation.[30] Paraffin-embedded section of the infected mice brain samples showed PHEV positive in the cytoplasm of nerve cell utilizing a mouse anti-PHEV monoclonal antibody by IFA. Antigen-positive neurons were widely distributed in the hippocampus and cerebral cortex in the brain.[30] Indeed, the transfer of this CoV to neurons has been manifested by the earlier reports in ultrastructural studies on the clathrin–coat mediated endocytotic or exocytotic pathways.[26] Recently, Li et al[36,37] has discussed the neuroinvasive potency of SARS-CoV-2 that cause respiratory failure in COVID-19 patients.

Considering all these, the neuroinvasive propensity has been manifested as a common feature of CoVs. Based on more similarity between SARS-CoV and SARS-CoV-2, COVID-19 may also have a similar potential. Recently, a study carried out by Mao et al[38] on COVID-19 infected 214 patients found that around 88% of severe patients showed neurological manifestations like acute cerebrovascular disease (impaired consciousness). It is very important to note the fact that, previous reports[7,10,13] discussed above has documented few SARS-CoV-2 infected patients showed neurologic symptoms like nausea, headache, and vomiting. However, more convincing evidence for brain illness caused by COVID-19 would include type 2 respiratory failure or specific focal neurological defects.[39] This should be established by virus detection in cerebrospinal fluid by polymerase chain reaction (PCR) or viral culture.

5 | REMARKS ON THE NEUROINVASIVE PROPENSITY OF SARS-CoV-2

Patients with acute SARS-CoVs infection have shown the presence of the virus in cerebrospinal fluid.[30] Baig et al[40] have recently published an article where they suggested a putative transcrbrial SARS-CoV-2 route to the brain and emphasized that SARS-CoV-2 RNA isolation in the cerebrospinal fluid would be the conclusive evidence to report the COVID-19 neurovirulence. In SARS patients, the neuromuscular disorder has considered as a critical illness neuropathy and myopathy.[41] Besides, more direct evidence has been reported in few countries. A COVID-19 case with encephalitis was reported in a male patient (age 56 years) on 16th March 2020 in Beijing Ditan Hospital, Capital Medical University, China (http://www.bjdth.com/html/1/151/163/3665.html). It is very important to note that the PCR amplification showed that the cerebrospinal fluid sample from the patient turned positive for SARS-CoV-2.

According to Turtle,[39] respiratory failure alone does not indicate CNS invasion by SARS-CoV-2. He also considers that several viruses can occasionally gain entry into the human CNS. Nataf[42] thinks that an alteration in the dopamine synthetic pathway is possibly involved in the COVID-19 pathophysiology. The mechanism implicit in the neurological symptoms is not clear which needs further studies, but the SARS-CoV-2 RNA isolation in the cerebrospinal fluid indicates that it might be naturally neuroinvasive in human beings. Since a clear understanding of SARS-CoV-2 is still missing, a high alert is needed for the possible involvement of CNS in COVID-19 patients, despite only a few cases are being documented with encephalitis or meningitis related COVID-19. Indeed, the role in the blood-brain barrier comprising the virus and avoiding it for gaining access to the neural tissue needs to be explored further in COVID-19 patients. Hence, the possible neuroinvasion may be a guiding significance to treat and prevent COVID-19.

6 | ROUTE OF TRANSMISSION

The epidemiological investigation in Wuhan, China has identified the outbreak which was associated with Huanan seafood market, where the majority of patients had visited or worked and subsequently closed for disinfection. Notably, a variety of live wild animals including fish, snakes, badgers, hedgehogs, birds (turtledoves), and animal meat were available in the market before the outbreak began.[43] Indeed, as the outbreak started, the main mode of transmission of the infection was from person-to-person. However, understanding of the transmission risks is incomplete. Person-to-person spread of SARS-CoV-2 infection is believed to occur mainly via respiratory droplets, corresponding to the spread of the influenza virus. With the droplet transmission, the virus released in the respiratory secretions when an infected person sneezes, coughs, or talks can infect other people if it makes direct contact with the mucous membrane. The infection can also occur when a person touches an infected surface and later touches their nose, mouth or eyes. Droplets usually do not travel more than 2 m and do not linger in the air. However, according to Van et al[44] SARS-CoV-2 remains for at least 3 hours in aerosols under certain experimental conditions. Taken all these into account, airborne precautions are highly recommended in many countries.

7 | CLOSING OPINION AND A PATH FORWARD

The SARS-CoV-2 outbreak has once again spotlighted the need to discover new vaccines, rapid development, and implementation of diagnostic tests against infectious diseases of the global health crisis. Indeed, further studies on COVID-19 and its pathogenesis will provide some guidance to deal with this rapidly spreading pandemic infectious disease. Several challenges remain as key areas, including the recent people who have tested COVID-19 positive. Can the cured patient be transmitted to others? All these indicate that more detailed criteria are needed for the prevention and control of SARS-CoV-2 virus and strong rigorous criteria to discharge patients after treatment. It is expected that the differences in the sequence of spike proteins between COVID-19 virus and SARS-CoV will enable scientists to identify epitopes in COVID-19 virus for the development of monoclonal antibodies against this virus. Basic research studies on SARS-CoV-2-host interactions is the key to several unanswered questions in the prevention and control of the disease. Many important questions about the identification and mechanism of interferon antagonists encoded by COVID-19 yet to be answered.

ACKNOWLEDGMENTS

The authors thank all the medical healthcare specialists who treated patients during this ongoing pandemic situation across the Globe. Dr. H. C. Yashavantha Rao also acknowledges the award from the University Grants Commission, New Delhi, Government of India (DSKPDF Scheme-No.F.4-2/2006 (BSR)/BL/17-18/0234).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

H.C. Yashavantha Rao http://orcid.org/0000-0001-6010-0781

Chelliah Jayabaskaran http://orcid.org/0000-0002-3634-0352

REFERENCES

1. Mukherjee S. Emerging infectious diseases: epidemiological perspective. *Indian J Dermatol*. 2017;62(5):459.
2. Zhu N, Zheng D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *New Engl J Med*. 2020;382(8):727-733.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565-574.
4. Gorbalenya AE, Baker SC, Babic RS, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses—a statement of the Coronavirus Study Group. *bioRxiv*. 2020. https://doi.org/10.1101/2020.02.07.937862. (In press).
5. World Health Organization: Emergencies: Coronavirus disease 2019 (COVID-19) Situation Report–90. Accessed on April 19, 2020.
6. Khan S, Ali A, Siddique R, Nabi G. Novel coronavirus is putting the whole world on alert. *J Hosp Infect*. 2020;104(3):252-253.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
8. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. https://doi.org/10.1001/jama.2020.1585
10. Talbot PJ, Ekandé S, Cashman NR, Mounir S, Stewart JN. Neurotropism of human coronavirus 229E. *Adv Exp Med Biol*. 1993;342:339-346.
11. Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J Immunol*. 2004;173:4030-4039.
12. Li K, Wohlford-Lenane C, Perlman S, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal dis-ease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis*. 2016;213:712-722.
13. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol*. 2018;92(7):1–21. https://doi.org/10.1128/JVI.00404-18
14. Li YC, Bai WZ, Hirano N, Hayashida T, Hashikawa T. Coronavirus infection of rat dorsal root ganglia: ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. *Virus Res*. 2012;163:628-635.
15. Mengeling WL, Boothe AD, Ritchie AE. Characteristics of a coronavirus (strain 67N) of pigs. *Am J Vet Res*. 1972;33(2):297-308.
16. Andries K, Pensaert MB. Immunofluorescence studies on the pathogenesis of hemagglutinating encephalomyelitis virus infection in pigs after oronasal inoculation. *Am J Vet Res*. 1980;41(9):1372-1378.
17. Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res*. 2000;87(5):E1-E9.
18. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA ex-pression profiling of ACE 2, a novel homologue of angiotensin con-verting enzyme. *FEBS Lett*. 2002;532:107-110.
19. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, Van-Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631-637.
20. Mattern T, Scholz W, Feller AC, Flad HD, Ulmer AJ. Expression of CD26 (dipeptidyl peptidase IV) on resting and activated human T-lymphocytes. *Scand J Immunol*. 1991;33:737-748.
21. Boonacker E, Van Noorden CJ. The multifunctional or moonlighting protein CD26/DPPIV. *Eur J Cell Biol*. 2003;82:53-73.
22. Bernstein HG, Dobrowolny H, Keilhoff G, Steiner J. Dipeptidyl peptidase IV, which probably plays important roles in Alzheimer disease (AD) pathology, is upregulated in AD brain neurons and associates with amyloid plaques. *Neurochem Int*. 2018;114:55-57.
23. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol*. 2004;203:622-630.
24. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 2005;202(3):415-424.
25. Xu J, Zhong S, Liu J, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis*. 2005;41:1089-1096.
26. Li YC, Bai WZ, Hirano N, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. *J Comp Neurol*. 2013;521:203-212.
27. Matsuda K, Park CH, Sunden Y, et al. The vagus nerve is one route of transneural invasion for intranasally inoculated influenza a virus in mice. *Vet Pathol*. 2004;41:101-107.
28. Chasey D, Alexander DJ. Morphogenesis of avian infectious bronchitis virus in primary chick kidney cells. *Arch Virol*. 1976;52:101-111.
29. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol*. 2008;82:7264-7275.
30. Li Z, He W, Lan Y, et al. The evidence of porcine hemagglutinating encephalomyelitis virus induced nonsuppurative encephalitis as the cause of death in piglets. *Peer J*.2016;4:e2443.
31. McCray PBJr, Pewe L, Wohlford-Lenane C, et al. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J Virol*. 2007;81:813-821.
32. Andries K, Pensaert M. Vomiting and wasting disease, a coronavirus infection of pigs. *Adv Exp Med Biol*. 1981;142:399-408. https://doi.org/10.1007/978-1-4757-0456-3_33
33. Mengeling WL, Boothe AD, Ritchie AE. Characteristics of a coronavirus (strain 67N) of pigs. *Am J Vet Res*. 1972;33:297-308.
34. Andries K, Pensaert MB. Immunofluorescence studies on the pathogenesis of hemagglutinating encephalomyelitis virus infection in pigs after oronasal inocula-tion. *Am J Vet Res*. 1980;41:13721378.
35. González JM, Gomez-Puertas P, Cavanagh D, Gorbalenya AE, Enjuanes L. A comparative sequence analysis to revise the current taxonomy of the family coronaviridae. *Arch Virol*. 2003;148:2207-2235.
36. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92:552-555. https://doi.org/10.1002/jmv.25728
37. Li Y, Bai WZ, Hashikawa T. Response to Commentary on: "The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients". *J Med Virol*. 2020:1-3.
38. Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *Med Rxiv*. 2020. https://doi.org/10.1101/2020.02.22.20026500. (In press).
39. Turtle L. Respiratory failure alone does not suggest central nervous system invasion by SARS-CoV-2. *J Med Virol*. 2020:1-2. In Press.
40. 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;11:995–998. https://doi.org/10.1021/acschemneuro.0c00122
41. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*. 2005;14:113-119.

42. Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. *J Med Virol*. 2020:1–2. https://doi.org/10.1002/jmv.25826
43. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579:265-269. https://doi.org/10.1038/s41586-020-2008-3
44. Van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020;382:1564–1567.

How to cite this article: Yashavantha Rao HC, Jayabaskaran C. The emergence of a novel coronavirus (SARS-CoV-2) disease and their neuroinvasive propensity may affect in COVID-19 patients. *J Med Virol*. 2020;1–5.
https://doi.org/10.1002/jmv.25918