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Neuroinvasive Coronaviruses

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ABSTRACT

Following the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), another highly pathogenic coronavirus named SARS-CoV-2 (previously known as 2019-nCoV) emerged in December 2019 in Wuhan, China, and rapidly spreads around the world.

Several recognized respiratory viral agents have a neuroinvasive capacity since they can spread from the respiratory tract to the Central Nervous System (CNS). Once there, infection of CNS cells (neurotropism) could lead to human health problems, because they are naturally neuroinvasive and neurotropic, human coronaviruses are suspected to participate in the development of neurological diseases.

Therefore, collecting new data will be instrumental to our understanding of how the ubiquitous human coronaviruses, given the proper susceptibility conditions and proper virus evolution and infection conditions, could participate in the induction or exacerbation of human neuropathologies. In the present study, we deduct the Severe Acute Respiratory Syndrome Coronavirus in the Brain.

Keywords:

Human coronavirus, Respiratory viral infection, Neuroinvasion, CNS infection, Neurological diseases.

Introduction

Viral infections of the respiratory tract represent a major problem for human and animal health around the world. These respiratory infections induce the most common illnesses [1]. Neuroinvasive viruses can damage the CNS as a result of misdirected host immune responses (virus-induced neuroimmunopathology) and/or viral replication, which directly induces damage to CNS cells (virus-induced neuropathology).

The Knowledge of mechanisms and consequences of virus interactions with the nervous system is essential to better understand potentially pathological consequences and design intervention strategies that are appropriate to encephalitis possibly caused by viral replication occurs in the brain tissue itself, possibly causing destructive lesions of the gray matter [2]. Or exacerbations of other types of neurological diseases for which a given virus is involved.

Coronaviruses: An overview

Virology

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes *Coronaviridae, Arteriviridae, Mesoniviridae,* and *Roniviridae* families.The *Coronavirinae* are further subdivided into four genera, the alpha, beta, gamma, and delta coronaviruses. Two of these human coronaviruses are α-coronaviruses, HCoV-229E, and HCoV-NL63, while the other two are β-coronaviruses,

HCoV-OC43 and HCoV-HKU1. HCoV-229E and HCoV-OC43 were isolated nearly 50 years ago [3], while HCoV-NL63 and HCoV-HKU1 have only recently been identified following the SARS-CoV outbreak [4-5]. Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy [6-7].

Coronavirus is an enveloped, positive single-strand RNA virus. It belongs to the Orthocoronavirinae subfamily, as the name, with the characteristic “crown-like” spikes on their surfaces[8]. Together with SARS-CoV, bat SARS-like CoV and others also fall into the genus beta-coronavirus.

Pathogenesis

Before the SARS-CoV outbreak, coronaviruses were only thought to cause mild, self-limiting respiratory infections in humans. These viruses are endemic in the human population, causing 15–30 % of respiratory tract infections each year. They cause more severe diseases in neonates, the elderly, and individuals with underlying illnesses, with a greater incidence of lower respiratory tract infection in these populations.

coronaviruses typically result in respiratory and enteric infections affecting both animals and humans and were considered relatively benign to humans before the severe acute respi¬ratory syndrome (SARS-CoV) outbreak in 2002 and 2003 in China [9]. A decade later, Middle East respiratory syndrome coronavirus (MERS-CoV), another patho¬genic coronavirus with a clinical picture reminiscent of SARS, was isolated in patients presenting with pneumonia in the Middle Eastern countries [10]. Just recently, in December 2019, a novel coronavirus (2019-nCoV) has emerged in Wuhan, Chi¬na, and has turned into a global health con¬cern [11].

In December 2019, novel coronavirus pneumonia emerged in Wuhan, China, linked initially to animal-to-human transmission in local wet markets. Subsequently, human-to-human transmission of the virus commenced, resulting in widespread respiratory illness in Wuhan and other urban areas of Hubei Province, China. The coronavirus then spread across China and at least 20 other nations [12]. On February 11, the World Health Organization named the virus SARS-CoV-2 and the syndrome

was named COVID-19, or coronavirus disease 2019 [13]

Mode of transmission

How easily the virus is transmitted between persons, and how it affects individual persons and potentially vulnerable population subgroups, such as the elderly or those with chronic health conditions? What is the source of the virus? And how can it spread around the world in such a short time? At the moment, we know relatively little about CoVID-19, except that it is a highly pathogenic human pathogen, possibly a zoonotic agent. There is limited knowledge regarding the transmission of COVID-19. The transmission has been confirmed to occur from human to human, and it is thought to be spread through respiratory droplets from coughs or sneezes [14].

Primary cases of COVID-19 have been traced back to the Huanan seafood market, with secondary cases occurring at hospitals among nurses and physicians who had extensive contact with COVID-19 patients. Furthermore, several individuals who did not have direct contact with the Huanan seafood market were diagnosed with the disease.

Clinical Manifestations and Diagnosis

Overall, an infection caused by the 2019- nCoV shares many clinical similarities with infection caused by SARS-CoV. A typical human coronavirus has an incuba¬tion period of 2–4 days; it is estimated to be 3–6 days for the 2019-nCoV, and 4–6 days for SARS-CoV.15, Infection with 2019-nCoV, similar to SARS-CoV, pres¬ents with non-specific symptoms such as fever, headache, cough, dyspnea, myalgia, and anosmia, some develop acute respiratory distress syndrome about a week into the illness which can result in death [16]. Rhabdomyolysis can be a late complication of the infection [17].

The mortality rate is about 3-4%. Terminally, patients go into a coma which is thought to be due to hypoxia or multi-organ failure. Chest X-ray examination In the early stage of pneumonia cases, chest images show multiple small patchy shadows and interstitial changes [18], remarkable in the lung periphery. Severe cases can further develop to bilateral multiple ground-glass opacity, infiltrating shadows, and pulmonary consolidation, with infrequent pleural effusion. While Chest CT scan Pulmonary lesions are shown more clearly by CT than X-ray examination, including ground-glass opacity and segmental consolidation in bilateral lungs, especially in the lung periphery. The CT features of COVID-19 need to be differentiated from those due to adenovirus pneumonia, influenza A (H1N1), and Severe Acute Respiratory Syndrome (SARS). Adenovirus pneumonia mostly occurs in children and mainly involves the middle and inner part of both lungs. So, laboratory diagnosis is necessary. The identification of COVID-19 mainly includes virus isolation and viral nucleic acid detection.

According to the traditional Koch`s postulates, virus isolation is the “gold standard” for virus diagnosis in the laboratory [19]. A variety of specimens (such as swabs, nasal swabs, nasopharynx or trachea extracts, sputum or lung tissue, blood, and feces) should be retained for testing on time, which gives a higher rate of positive detection of lower respiratory tract specimens [19].

Treatments and Preventions

At present, there is no vaccine or antiviral treatment for human and animal coronavirus, so that identifying the drug treatment options as soon as possible is critical for the response to the CoVID-19 outbreak. WHO has announced that a vaccine for SARS-CoV-2 should be available in 18 months, but achieving this will require funding and public interest to be maintained even if the threat level falls [20]. The mainstay of clinical management is largely symptomatic treatment, with organ support in intensive care for seriously ill patients [20]. After the treatment, if the patient’s condition improved significantly and there were no respiratory symptoms of fever or cough, the patient would be discharged after passing two consecutive nucleic acid tests

Human coronaviruses in the CNS

The respiratory involvement of HCoV has been established since the 1960s. Also, for almost four decades now, the scientific literature has demonstrated that HCoV is neuroinvasive and neurotropic and could induce an overactivation of the immune system, in part by participating in the activation of autoreactive immune cells that could be associated with autoimmunity in susceptible individuals. Furthermore, it was shown that in the murine CNS, neurons are the main target of infection, which causes these essential cells to undergo degeneration and eventually die by some form of programmed cell death after virus infection.

While SARS-CoV is considered a respiratory pathogen in humans, the virus has been detected in the brains of infected patients. Neuroinvasive viruses can damage the CNS as a result of misdirected host immune responses (virus-induced neuroimmunopathology) and/or viral replication, which directly induces damage to CNS cells (virus-induced neuropathology). In acute encephalitis, viral replication occurs in the brain tissue itself, possibly causing destructive lesions of the gray matter [2]. In one report, an examination of autopsy samples from eight patients with SARS revealed the presence of SARS-CoV in brain samples by immunohistochemistry, electron microscopy, and real-time reverse transcription-PCR [22].

This detection of HCoV RNA in human brain samples demonstrates that these respiratory pathogens are naturally neuroinvasive in humans and suggest that they establish a persistent infection in human CNS [23] but many unanswered questions remain. Could the headache be symbolic of viral meningitis? There is a report of the detection of the virus in CSF of one patient.

Does anosmia suggest an involvement of the olfactory bulbs? In mouse models of coronavirus encephalitis, the virus can enter the brain trans-neuronally through the olfactory pathways.4 Hence this relatively innocuous symptom could be indicative of a potentially more serious complication. Can respiratory syndrome be due to brainstem involvement? Brain imaging and pathological evaluation of the brain are necessary to understand the full impact of the virus. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome [24]. Previous studies found that coronavirus might be neurotropic, neuroinvasive, and neurovirulent, although it was first isolated as a pathogen of the respiratory tract [23,24]. At least 3 routes, including olfactory nerve, a hematogenous route, and lymphatic systems could be used by coronavirus to gain access to the CNS [8–25]. This extensive neuronal infection is the main cause of death because intracranial inoculation with low doses of virus results

in a uniformly lethal disease even though little infection is detected in the lungs.

Death of the animal likely results from dysfunction and/or death of infected neurons, especially those located in cardiorespiratory centers in the medulla. Remarkably, the virus induces minimal cellular infiltration in the brain. Our results show that neurons are a highly susceptible target for SARS-CoV and that only the absence of the host cell receptor prevents severe murine brain disease. The cell lines of astrocytoma, neuroblastoma, neuroglioma, and oligodendrocyte were all susceptible to the infection of human coronaviruses [23-26]. Mouse hepatitis virus, a murine coronavirus, has been found to induce demyelinating disease of the CNS [27-28].

Discussion and Conclusion

The presence of coronaviruses in the human central nervous system is now a recognized fact as they appear to be part of a viral flora of the brain, with potential neuropathological consequences in genetically or otherwise susceptible individuals, If the neuroinvasion of SARS-CoV-2 does take a part in the development of respiratory failure in COVID-19 patients, the precaution with masks will be the most effective measure to protect against the possible entry of the virus into the CNS.

However, further basic research that helps decipher complex underlying mechanisms involved in virus-host-cell interactions is warranted and will be instrumental to our understanding of how coronaviruses that infect human beings, given the proper susceptibility conditions and proper virus evolution and infection conditions, may induce neuronal degeneration and could participate in the induction or exacerbation of human neuropathologies. In the past century, we have made tremendous progress in the prevention, diagnosis, and treatment of diseases. The time to take action is now, we can image the brain and its networks with exquisite precision and we can fix mutated genes before they can cause harm.

Conflict of Interest:

There are no conflicts of interest.

References

1. Vareille M, Kieninger E, Edwards MR, et al. (2011) The airway epithelium: soldierin the fight against respiratory viruses. Clin Microbiol Rev. 24(1): pp. 210-229.

2. Talbot PJ, Desforges, M, Brison, E, et al. (2011) Coronaviruses as Encephalitisinducing infectious agents. In: Tkachev S (ed) Non-flavirus Encephalitis. In-Tech, pp. 185-202.

3. Hamre D, Procknow JJ (1966) A new virus isolated from the human respiratory tract. Proc Soc Exp Biol Med 121(2): pp. 190-193.

4. Woo PC, Lau SK, Chu CM, et al. (2005) Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol. 79(1): pp. 884-895.

5. Van Hoek L, Pyrc K, Jebbink MF, et al. (2004) Identification of a new human coronavirus. Nat Med. 10(1): pp. 368-373.

6. Barcena M, Oostergetel GT, Bartelink W, et al (2009) Cryo-electron tomography of mouse hepatitis virus: insights into the structure of the coronavirion. Proc Natl Acad Sci USA.106(1): pp. 582–587

7. Neuman BW, Adair BD, Yoshioka C, et al (2006) Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. J Virol. 80(5): pp. 7918-7928.

8. Perlman S (2020) Another decade, another coronavirus. N Engl J Med. 2020(4); 382:pp. 760-762.

9. Zhong NS, Zheng BJ, Li YM, et al. (2003) Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in Febru¬ary, 2003 Lancet. 362(8): pp. 1353-1358.

10. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 367(2): pp. 1814-1820.

11. Zhu N, Zhang D, Wang W, et al. (2020) A novel coronavirus from patients with pneumonia in China,. N Engl J Med. 382: pp. 727-733.

12. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 382: pp. 1199-1207.

13. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Accessed February 13, 2020.

14. Huang C, Wang Y, Li X, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 395(1): pp. 497–506.

15. Knipe DM, Howley PM (2007) Fields' Virology. vol 1. 5th Edition. Wolters Kluwer,

16. Zhou F, Yu T, Du R, et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 395(10229): pp. 1054-1062

17. Jin M, Tong Q (2020) Rhabdomyolysis as potential late complication associated with 2019 novel coronavirus disease. Emerg Infect Dis. 26(7):102-108.

18. Chaolin H, Yeming W, Xingwang L, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 395(3): pp. 497-506.

19. Yu F, Du L, Ojcius DM, et al. (2020) Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes Infect. 22(2): pp. 74-79

20. Diseases TLI (2020) Challenges of coronavirus disease 2019. The Lancet Infectious Diseases. 20(3): pp. 261.

21. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. The Lancet 2020; 395:e35-e6.

22. Gu JE, Gong B (2005) Zhang,and all Multiple organ infection and the pathogenesis of SARS. J Exp Med. 202(3): 415-424.

23. Arbour N, Day R, Newcombe J, Talbot PJ (2000) Neuroinvasion by human respiratorycoronaviruses. J Virol 74(19):8913–8921

24. Compton SR, Barthold SW, Smith AL (1993) The cellular and molecular pathogenesis of coronaviruses. Lab Anim Sci. 43(1): pp. 15–28.

25. Barthold SW, Smith AL (1992) Viremic dissemination of mouse hepatitis virus-JHM following intranasal inoculation of mice. Arch Virol. 122(7): pp. 35–44.

26. Barac-Latas V, Suchanek G, Breitschopf H, et al. (1997) Patterns of oligodendrocyte pathology in coronavirus-induced subacute demyelinating encephalomyelitis in the Lewis rat. Glia.19(2): pp. 1–12.

27. Watanabe R, Wege H, Ter Meulen V (1983) Adoptive transfer of EAE-like lesions from rats with coronavirus-induced demyelinating encephalomyelitis. Nature. 305(1): pp. 150-153.

28. Fleming JO, Trousdale MD, Bradbury J, et al. (1987) Experimental demyelination induced by coronavirus JHM (MHV-4): molecular identification of a viral determinant of paralytic disease. Microb Pathog. 3(1):9-20.