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Neuroinvasion of COVID-19 pandemic: New Findings.

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ABSTRACT

The fast coronavirus pandemic invasion (COVID19) attributed to severe acute respiratory syndrome by coronavirus-2 (SARSCoV2) is becoming an international major health problem. It has been defined as a worldwide pandemic by the largest international health organization (the World Health Organization (WHO) last March this year. Nearly all COVID-19 patients have dyspnea as the most prominent symptom. Neurologic manifestations may also present such as anosmia, headache, confusion, encephalitis Guillain Barre syndrome, and cerebrovascular stroke. Coronaviruses are well known to be neuroinvasive. Accumulating proof is present that coronaviruses disease is not a consistently restricted area of the respiratory system. The nervous system may be involved in vulnerable patients and may cause severe complications and death. Hyposmia is the most common peripheral neurological manifestation. Post-infectious, autoimmune complications in the recovery period may also happen. It is of high importance to understand and identify neurologic burden of helping treatment strategies as the current pandemic continues to grow. Many recent reports confirmed central nervous system involvement in COVID-19 infected patients. We will try to explore the neurologic symptoms and complications of the new mysterious outbreak.

Introduction

COVID-19 disease responsible virus is a member of Coronaviruses group [1]. It is a virus with a diameter equals 60–140 nm. It has only one RNA strand which has an envelope[2]. Its sheath made up of two lipid layers with four protein components recognized as N (nucleocapsid), E (envelope), S (spike), and M (membrane) [1]. The infected cell receptor and (S) protein connection is crucial for viral infection [3]. (SARSCoV2) has the feature of being a part of the group of the genus Beta-coronavirus (β-CoV) which is like the Middle-East viral respiratory syndrome by the coronavirus (MERS-CoV) as well as severe acute respiratory syndrome by the coronavirus (SARSCoV) – the source of SARS global epidemic at 2003 [4]. Spike protein mutation is in charge the re-evolution of the SARSCoV-2 world-wide outbreak [5]. Rapid transmission of coronaviruses was discussed before, and neurologic complications may happen due to indirect, direct, and post-infectious effects[6].

Pathophysiology

Macrophages and T cells are attacked by the SARS-CoV directly after attacking lung epithelial cells causing lymphopenia reducing CD8+ and CD4+ numbers and disturbed acquired immune response [3]. Cytokine storm is an exaggerated immune reaction in which huge amounts of inflammatory immunocytokines. Interleukin-6 (IL-6)

may be the main cause of severe inflammation and cell death [7]. The virus makes his way by mucous membranes, up to lungs crossing the respiratory system. It attacks specific receptors (angiotensin-converting enzyme 2 (ACE2) expressed in differ-rent body systems like respiratory, urinary, cardiac, and GIT systems [8]. Post-infection autoimmune response might happen in which adaptive immune response becomes directed against host epitopes causing tissue damage after the virus has been cleared [6]. In addition to inflammatory mechanism, thrombosis and pulmonary embolism have been observed in severe form of COVID 19. Elevated Troponin, d-dimer and fibrinogen levels were observed in severe cases. The hypercoagulable profiles seen in severe COVID 19 patients likely should indicate significant endothelial injury and losing the endothelium function of vasodilation, fibrinolysis, and anti-aggregation. Of note, the endothelial cells also express ACE2 [9]. CNS invasion has multiple possible mechanisms. Firstly, ACE-2 receptors are also found in glial cells in brain and spinal neurons. Hence it can attach, multiply and damage the neuronal tissue [10]. Secondly, disruption of blood brain barrier during the viremia causes the virus to enter the brain directly and /or through the synapse. Moreover, COVID 19 virus could invade the peripheral nerve terminals by which have access to the CNS [11]. At last, increased invasion of coronavirus to macrophages triggers macrophage and cytokines secretion [3]. This may result in macrophages trans passing to the nervous system and attacking myelin sheath and neurons [12].

Neurologic Manifestations

Coronaviruses are mainly implicated in respiratory and gastrointestinal diseases [1]. The last Chinese outbreak reported 44,500 COVID-19 patients. 81% of cases had pneumonia, 14% had severe lung symptoms shortness of breath, and hypoxemia. Five percent had respiratory failure and other organs failure [13]. Systemic complications consisted of heart failure, and septic shock [14]. Neurologic manifestations were present in nearly 100 patients in Wuhan, China outbreak including disturbed level consciousness in 9% of patients and headache in 8% of patients[4]. Another study reported that 35.9% of patients were firstly presented by neurological complaints including headache, impaired conscioussness, stroke, and seizures [15]. Kidney, liver, and cardiac injury may contribute to consequent neurological symptoms of COVID-19[16]. Also, Cytokine storm, hypercoagulability, arrhythmias, and cardiac failure which are major stroke etiologies[14].

Primary Neurologic manifestations.

Infected brain tissues by viral RNA was found post-mortem is clear evidence of viral CNS invasion [17]. Viral presence in CSF is also proved in severely ill patients [16]. CNS invasion mechanisms by SARS-CoV are still unclear. It may happen by nasal epithelial destruction then through the olfactory bulb [6]. Anosmia and taste sensation loss are among the early manifestations of COVID-19 infection [18]. Hyposmia is the most common peripheral neurological manifestation [19]. Anosmia post viral infection is a common cause of smell loss and is known to be associated with many human viral strains, including other coronaviruses [20]. Many reports evaluating mechanisms of COVID-19 – mediated smell sensation loss have suggested neurotrophic targeting of olfactory neurons vs infection of non-neural olfactory epithelial cells [21]. A recent report revealed two infected patients were firstly presented with

Guillain-Barré syndrome (GBS) variant and multiple cranial neuropathies. One patient presented with ophthalmoplegia, ataxia, and areflexia Miller Fisher Syndrome. The other one was presented with bilateral abducens paralysis and ageusia [22]. Also, hypoxic brain injury is a major mechanism of CNS damage secondary to respiratory failure [23]. COVID-19 patients are often complicated with high risk of cerebrovascular diseases, such as cardio-cerebrovascular disease, hypertension, and diabetes [24] or death, occurring mainly in elderly and chronically ill patients [25].Estimated incidence of implicated health problems among COVID-19 patients in USA revealed that 0.7% of COVID-19 patients had underlying neurologic problems [26].

Secondary autoimmune neurologic manifestations

A recent report has revealed the first diagnosed COVID-19 with acute hemorrhagic encephalitis [27]. It shows the first case of COVID-19–associated acute necrotizing hem-orrhagic encephalopathy which is a rare encephalopathy that has been associated with other viral infections. Another report showed the diagnosis of Guillain-Barré syndrome was establ-ished in the presentation of an infected patient with COVID19. The timing association between the infection and appearance of acute polyneuropathy Considered that infection was a direct cause of autoimmune polyneuritis [28].

The Existence of coronaviruses in the nervous system after the acute infection, may be responsible for immune induced inflammation and demyelination in vulnerable patients [6]. The appearance of Human CoV RNA particles in CSF of patients with acute demyelinating encephalomyelitis [29] and disseminated sclerosis [30] supports that theory.

Human-CoV infections also caused post-infection immune-mediated syndromes, such as GBS and encephalitis [31]. This may be attributed to the molecular similarity between Human-CoV and myelin basic protein(MBP) [32]. Interestingly, it was revealed that the infecting virus interacts with certain receptors [angio-tensin-converting enzyme-2 (ACE-2) receptors]. They are the main gate for host cellular invasion. This discovery lightens up the question whether ACE2 receptors expression inside the nervous system can influence the presumed role of SARS-CoV in damage to CNS and neurological complications and mortality [16].

CONCLUSION

During exploring the new Covid-19 pandemic across the world the awareness about COVID-19 neurologic burden as regard presentation and further complications must have high consideration due to the progressing accumulating evidence of CNS involvement during viral infection. The exact function of ACE-2 receptors in the COVID-19 infection raises the questions and concerns about the nature CNS involvement in COVID-19 infection.

References

1. Li, Y.C., W.Z. Bai, and T. Hashikawa, *The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients.* Journal of medical virology, 2020.
2. Rothan, H.A. and S.N. Byrareddy, *The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak.* Journal of autoimmunity, 2020: p. 102433.
3. Dandekar, A.A. and S. Perlman, *Immunopathogenesis of coronavirus infections: implications for SARS.* Nature reviews immunology, 2005. **5**(12): p. 917-927.

4. Chen, N., et al., *Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.* The Lancet, 2020. **395**(10223): p. 507-513.
5. Wang, C., et al., *The establishment of reference sequence for SARS-CoV-2 and variation analysis.* Journal of medical virology, 2020.
6. Desforges, M., et al., *Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?* Viruses, 2020. **12**(1): p. 14.
7. Prompetchara, E., C. Ketloy, and T. Palaga, *Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic.* Asian Pac J Allergy Immunol, 2020. **38**(1): p. 1-9.
8. Chen, C., et al., *Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies.* Zhonghua shao shang za zhi= Zhonghua shaoshang zazhi= Chinese journal of burns, 2020. **36**: p. E005-E005.
9. Wang, M., et al., *Thrombotic regulation from the endothelial cell perspectives.* Arteriosclerosis, thrombosis, and vascular biology, 2018. **38**(6): p. e90-e95.
10. de Kloet, A.D., et al., *Role of neurons and glia in the CNS actions of the renin-angiotensin system in cardiovascular control.* American journal of physiology. Regulatory, integrative and comparative physiology, 2015. **309**(5): p. R444-R458.
11. Li, Y.-C., W.-Z. Bai, and T. Hashikawa, *Response to Commentary on "The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients".* Journal of Medical Virology, 2020. **92**(7): p. 707-709.
12. Kim, T.S. and S. Perlman, *Viral expression of CCL2 is sufficient to induce demyelination in RAG1−/− mice infected with a neurotropic coronavirus.* Journal of virology, 2005. **79**(11): p. 7113-7120.
13. Wu, Z. and J.M. McGoogan, *Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention.* Jama, 2020.
14. Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* The Lancet, 2020.
15. Mao, L., et al., *Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study.* 2020.
16. Baig, A.M., et al., *Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms.* ACS chemical neuroscience, 2020.
17. Ding, Y., et al., *Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways.* The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 2004. **203**(2): p. 622-630.
18. Giacomelli, A., et al., *Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study.* Clin Infect Dis, 2020. **70**.
19. Montalvan, V., et al., *Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review.* Clinical neurology and neurosurgery, 2020. **194**: p. 105921-105921.
20. Suzuki, M., et al., *Identification of viruses in patients with postviral olfactory dysfunction.* The Laryngoscope, 2007. **117**(2): p. 272-277.
21. Baig, A.M., et al., *Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms.* ACS chemical neuroscience, 2020. **11**(7): p. 995-998.

22. Gutiérrez-Ortiz, C., et al., *Miller Fisher Syndrome and polyneuritis cranialis in COVID-19.* Neurology, 2020.
23. Tu, H., et al., *Current epidemiological and clinical features of COVID-19; a global perspective from China.* J Infect, 2020. **81**(1): p. 1-9.
24. Bai, Y., et al., *Presumed asymptomatic carrier transmission of COVID-19.* Jama, 2020. **323**(14): p. 1406-1407.
25. Watkins, J., *Preventing a covid-19 pandemic*. 2020, British Medical Journal Publishing Group.
26. COVID, C., et al., *Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019—United States, February 12–March 28, 2020.* Morbidity and Mortality Weekly Report, 2020. **69**(13): p. 382.
27. Poyiadji, N., et al., *COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI.* Images in Radiology, 2020. **10**.
28. Zhao, H., et al., *Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence?* The Lancet Neurology, 2020.
29. Yeh, E.A., et al., *Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis.* Pediatrics, 2004. **113**(1): p. e73-e76.
30. Cristallo, A., et al., *Human coronavirus polyadenylated RNA sequences in cerebrospinal fluid from multiple sclerosis patients.* The new microbiologica, 1997. **20**(2): p. 105-114.
31. Algahtani, H., A. Subahi, and B. Shirah, *Neurological complications of Middle East respiratory syndrome coronavirus: a report of two cases and review of the literature.* Case reports in neurological medicine, 2016. **2016**.
32. Chew, F.T., S.Y. Ong, and C.L. Hew, *Severe acute respiratory syndrome coronavirus and viral mimicry.* The Lancet, 2003. **361**(9374): p. 2081.