World Journal of Clinical Medicine Research, 2022, 1, 386
www.scipublications.org/journal/index.php/wjcmr
DOI: 10.31586/wjcmr.2022.386

Brief Review

COVID-19 and Central Nervous System Diseases

Jiaxia Li [1,#], Yuan Feng [1,#], Mingwu Xia [1], Li Wan [2,3,4,*]

[1] The Second People's Hospital of Hefei; Hefei Hospital Affiliated to Anhui Medical University, Hefei, Anhui 230011, China

[2] Affiliated Psychological Hospital of Anhui Medical University; Hefei Fourth People's Hospital; Anhui Mental Health Center, Anhui 230026, China

[3] Anhui Branch of National Clinical Research Center for Mental Disorders, Anhui 230026, China

[4] Anhui Clinical Research Center for Mental Disorders, Anhui 230026, China

* Correspondence: Li Wan (wanli@ahmu.edu.cn)

Co-first Authors

Abstract: We reviewed the influence of coronavirus disease 2019 (COVID-19) on the central nervous system reported in the literature since its prevalence. Common neurological symptoms of COVID-19 include altered or impaired consciousness, headache, dizziness, cerebrovascular accidents, and seizures, etc. Encephalopathy caused by or related to COVID-19 includes stroke, acute encephalitis, and Guillain-Barre syndrome. Concomitant COVID-19 in patients with vascular risk factors increased the risk of stroke; the hypercoagulable state and vascular dysfunction caused by COVID-19 also led to stroke. Acute encephalitis was usually accompanied by a history of headache, fever, and altered mental status, and shown hemorrhagic lesions or high signal on MRI. In Guillain-Barre syndrome, there was a time lag between infection with the primary pathogen and the onset of neurological symptoms, which generally manifest as limb paralysis and various sensory abnormalities. The review illustrated that COVID-19 lead to serious consequences of brain and brought difficulties to the treatment. Exploring the neural mechanisms of COVID-19 to better understand the activity of the virus in the brain and to prevent further viral damage to the brain is an urgent issue.

Keywords: COVID-19, Central nervous system, Common neurological symptoms, Stroke, Guillain-Barre syndrome, Acute encephalitis

How to cite this paper:
Li, J., Feng, Y., Xia, M., & Wan, L. (2022). COVID-19 and Central Nervous System Diseases. *World Journal of Clinical Medicine Research*, *1*(1), 9–13. Retrieved from https://www.scipublications.com/journal/index.php/wjcmr/article/view/386

Received: July 10, 2022
Accepted: August 17, 2022
Published: August 19, 2022

1. Introduction

A new coronavirus has triggered a global pandemic since late 2019, and the disease caused by this new coronavirus was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). The most common clinical manifestations in patients with mild cases were fever, dry cough and other respiratory symptoms, while patients with severe cases presented with respiratory distress, sepsis, renal failure and heart failure, eventually leading to death. However, in addition to respiratory symptoms, an increasing number of studies have shown that COVID-19 causes potentially neurotropic disorders, ranging from mild symptoms such as hyposmia and headache and dizziness to severe symptoms such as stroke, epilepsy, encephalitis, and acute myelitis. In this study, we systematically reviewed the influence of COVID-19 on the central nervous system reported in the literature since its prevalence.

2. Common neurological symptoms

Several case reports have shown that COVID-19 patients exhibit neurological and psychiatric complications, such as altered consciousness and encephalopathy[1, 2]. An

early study of 214 hospitalized patients with COVID-19 in Wuhan, China, showed that more than one-third (36.4%) of patients had some degree of neurological involvement, but this was often underestimated and overlooked in clinical practice [3]. The study noted that headache and dizziness were the two most common central nervous system manifestations, accounting for 17% and 13%, respectively. In contrast, the incidence of more serious neurological complications, such as cerebrovascular accidents and seizures, was 3% and 0.5%, respectively. Those with severe COVID-19 infections were found to be more likely to have neurological complications. Interestingly, the study noted that most neurological manifestations occurred early in the course of the infection, and they might be important predictors of deterioration of clinical symptoms. Another retrospective study by Chen et al. showed symptoms of impaired consciousness (9%) and headache (8%) in 99 patients [4]. However, the incidence of neurological symptoms was significantly lower than that of typical respiratory symptoms, such as cough (82%) and dyspnea (31%). In a study of 219 patients, Li et al. emphasized that 5% of patients were complicated with severe cerebrovascular diseases, including 10 cases of cerebral infarction and 1 case of intracerebral hemorrhage, of which a considerable portion (6 cases) eventually died [5].

3. Stroke

Oxley et al. reported 5 cases of 50-year-old stroke patients with macroangiopathy diagnosed as COVID-19 and 2 younger cases aged 33 and 37 years without previous underlying disease [6]. A study from Wuhan reported 6 cases of stroke among 214 patients with COVID-19 [4]. In a retrospective study, 4 geriatric patients with multiple risk factors for cerebrovascular diseases were found to have concurrent strokes. The etiology was confirmed to be macrovascular lesions. Similarly, 5 cases of COVID-19 combined with stroke were reported, 3 of which were young patients with vascular risk factors, including diabetes, dyslipidemia and hypertension, all with evidence of large vessel occlusion. The apparent association between COVID-19 and the incidence of acute stroke may be because the two diseases share common risk factors. Studies have shown that the severity of COVID-19 infections is directly related to the presence of vascular diseases, such as hypertension, diabetes and macrovascular lesions, that predispose elderly individuals. For example, a study with 191 COVID-19 patients showed that the previous underlying medical history, including hypertensive disease and diabetes mellitus (30% and 19%, respectively), was followed by cardiovascular disease, accounting for 8% [7]. Among the 191 patients, 23% had combined heart failure, 20% had combined infectious shock, 19% had combined coagulopathy, and 17% had combined acute heart injury. In addition, a study suggested that the COVID-19-induced hypercoagulable state may be the most important pathogenesis of stroke in patients without vascular risk factors [8].

In cases of severe acute respiratory syndrome coronavirus infection, patients with vascular risk factors had complications such as arrhythmia cardiomyopathy, hypotension, shock, disseminated intravascular coagulation and heart failure, which further induced cardiogenic embolism, cerebral hypoperfusion and large vessel occlusion and increased the risk of stroke. The presence of specific viral factors directly contributes to a hypercoagulable state, arteritis and endothelial dysfunction, which can lead to ischemic stroke or cerebral hemorrhage.

4. Guillain-Barre syndrome

A number of confirmed cases of Guillain‐Barre syndrome have been reported in COVID-19 patients. In these cases, the characteristics of Guillain‐Barre syndrome and the typical respiratory symptoms of COVID-19 have considerable mutation. A study reported that the initial symptoms of Guillain‐Barre syndrome were mild fever, and 9 patients developed related symptoms, such as quadriplegia and paresthesia, after being

diagnosed with COVID-19 [9]. Although the initial symptoms of these COVID-19 patients varied, most reported patients had bilateral lower extremity weakness marked by limb paresis, loss of deep reflexes, and various sensory abnormalities. In those patients, some showed elevated levels of cerebrospinal fluid proteins.

Zhao et al. suggested that Guillain–Barre syndrome was a symptom caused by neocoronavirus, but it has not been confirmed if this was a coincidence or an association of symptoms [10]. There was a significant time lag between infection with the primary pathogen and the onset of neurologic symptoms in patients with Guillain–Barre syndrome, also known as the postinfection manifestation. This postinfection manifestation did not explain why there were specific patients who presented with complications of COVID-19, symptoms of neurological involvement, or the initial symptoms of Guillain–Barre syndrome. The study proposed a so-called "infection-like" model, in which Guillain–Barre syndrome occurred in combination with an acute infection. This might explain some of the early-onset cases of Guillain–Barre syndrome, some of which do not have significant respiratory infections prior to onset, or any other known history of infections that may cause Guillain–Barre syndrome. One case of Guillain–Barre syndrome overlapped with Bickerstaff encephalitis in a patient with Middle East respiratory syndrome [11], and another reported a 5-year-old child with Guillain–Barre syndrome after coronavirus infection [12]. Guillain–Barre syndrome appeared to be associated with the ongoing COVID-19 pandemic. However, the lack of relevant studies made it difficult to further explore the direct causal relationship between pathogens.

5. Acute encephalitis

A case-report study reported that a middle-aged woman with COVID-19 was diagnosed with hemorrhagic necrotizing encephalitis 3 days after presenting with cough, fever, and altered mental status, with hemorrhagic lesions in the bilateral thalamus, medial temporal lobe, and insula [13]. Another case report of a 24-year-old male who experienced headache, generalized fatigue and fever followed by a generalized seizure and impaired consciousness showed a high signal along the right subventricular wall, right temporal lobe and hippocampus on MRI, suggesting COVID-19-induced meningoencephalitis [14].

6. Discussion

It is worth noting that no study to date has determined whether neurological involvement is a predictor of poor prognosis in patients with COVID-19. To date, all studies on neurological involvement have been limited to severely ill patients hospitalized because of COVID-19. Such a population was more likely to have other serious concurrent diseases, which might affect the incidence of neurological symptoms. More studies with community-based patients with mild to moderate symptoms are needed to investigate the incidence of neurological and other extrarespiratory symptoms. Whether the neurological manifestations of COVID-19 are a direct result of the neuroinvasive properties of the virus or an indirect result of the ensuing multiorgan dysfunction and biochemical abnormalities needs to be further clarified.

The COVID-19 virus was a new mutant genus generation of severe acute respiratory syndrome coronavirus (SARS-CoV) and was called SARS-CoV-2 virus. With an ongoing mutation of the coronavirus species, the second generation was often more affinity to the human body than the first generation, with a stronger infection power. The exact route of entry of COVID-19 into the central nervous system is unknown. The COVID-19 virus, which belongs to the same beta coronavirus as SARS-CoV, is commonly neurophilic in nature, and once in the systemic circulation, it invades neural tissue by binding and

interacting with angiotensin-converting enzyme 2 (ACE2) receptors in the intracranial capillary endothelium via the stinger protein [15].

Previous studies have confirmed that beta coronaviruses enter the central nervous system in two ways [16-18]: first, through blood transmission, where the virus disrupts the capillary endothelium of the blood – brain barrier and enters the cerebral circulation; second, the virus is more likely to enter locally through the sieve bone, sieve plate and olfactory bulb. An increasing number of studies have shown that olfactory deficit is one of the symptoms of COVID-19, providing evidence that the virus enters the cranial brain through the olfactory nerve [19]. A study by Wrapp et al. on the structural integrity of the COVID-19 S protein showed that COVID-19 virus had a 10- to 20-fold increased affinity level for ACE2 compared to SARS-CoV, showing that although they were structurally similar, the two spinosomal proteins were not identical [20]. It has been shown that COVID-19 can indirectly cause neurological impairment through tissue hypoxia, ACE2, hypertension, coagulation disorders, and immune-mediated reactions. Coronaviruses have the ability to infect macrophages and glial cells [21-23]. Experimental models have shown that following coronavirus infection, glial cells are able to secrete proinflammatory factors such as interleukin 6, interleukin 12, interleukin 15, and tumor necrosis factor alpha.

7. Conclusion

COVID-19 has become a challenging problem to our world. The most typical symptoms were respiratory and neurological symptoms, which can lead to more serious consequences, such as the impairment of cognitive function and psychiatric disorders. In addition to the brain diseases mentioned in this article, such as stroke, Guillain – Barre syndrome, and acute encephalitis, recent studies have also reported sequelae of brain atrophy caused by neoconviruses. These caused serious disruptions in the lives of patients with neoconviruses and were a direction of research that must be of concern to us. However, whether COVID-19 is a new neurogenic disease or a secondary disease is still under debate, and the question of how it causes acute and chronic neurological changes remains unclear. Exploring the neural mechanisms of COVID-19 to better understand the activity of the virus in the brain and to prevent further viral damage to the brain is an urgent issue.

Availability of Data and Materials

NA

Conflicts of interest

The authors have no potential conflicts of interest to declare.

Funding

Anhui Medical University School Funding Project (2021xkj235) and Anhui Mental Health Center Research Project (HFSY202117).

Authors' Contributions

JL performed the literature search and drafted the manuscript. YF assisted with manuscript critique. LW edited the manuscript. All authors read and approved the manuscript before submission.

References

[1] Yin R, Feng W, Wang T, et al. Concomitant neurological symptoms observed in a patient diagnosed with coronavirus disease 2019. Journal of Medical Virology, 2020, 92(10): 1782-1784.

[2] Filatov A, Sharma P, Hindi F, et al. Neurological complications of coronavirus disease (COVID- 19): Encephalopathy. Cureus, 2020, 12: e7352.
[3] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurology, 2020, 77: 1-9.
[4] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020, 395: 507-513.
[5] Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke and Vascular Neurology, 2020, svn-2020-000431.
[6] Oxley T, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. The New England Journal of Medicine, 2020, 382: e60.
[7] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 2020, 395: 1054-1062.
[8] Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. Brain, Behavior and Immunity, 2020, 87: 115-119.
[9] Toscano G, Palmerini F, Ravaglia S, et al. Guillain–Barré Syndrome Associated with SARS-CoV-2. The New England Journal of Medicine, 2020, 382: 2574-2576.
[10] Zhao H, Shen D, Zhou H, et al. Guillain–Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? The Lancet Neurology, 2020, 19: 383-384.
[11] Kim J, Heo J, Kim H, et al. Neurological complications during treatment of middle east respiratory syndrome. Journal of Clinical Neurology, 2017, 13: 227-233.
[12] Sharma K, Tengsupakul S, Sanchez O, et al. Guillain–Barré syndrome with unilateral peripheral facial and bulbar palsy in a child: A case report. SAGE Open Medical Case Reports, 2019, 7: 2050313X1983875.
[13] Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology, 2020, 296: E119-E120.
[14] Moriguchi T, Harii N, Goto J, et al. A first case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. International Journal of Infectious Diseases, 2020, 94: 55-58.
[15] Netland J, Meyerholz DK, Moore S, et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. Journal of Virology, 2008, 82: 7264-7275.
[16] Sun Y, Wang H, Zhao M. Research progress on the relationship between cognitive dysfunction and blood‐brain barrier in COVID-19. Chinese Journal of Anesthesiology, 2022, 42 (01): 121-124.
[17] Yamagishi M, Fujiwara M, Nakamura H. Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. Rhinology, 1994, 32 (3): 113-118.
[18] Hu C, Yan T, Zhang J, et al. A case of COVID-19 pneumonia with olfactory and gustatory deficits as clinical manifestations. Journal of Shanghai Medicine, 2020, 43 (10): 581-583.
[19] Beltrán-Corbellini A, Chico-García J, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicenter PCR-based case–control study. European Journal of Neurology, 2020, 10: 1111.
[20] Wrapp D, Wang N, Corbett K, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science, 2020, 367: 1260-1263.
[21] Baig A M, Khaleeq A, Ali U, 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): 995-998.
[22] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurology, 2020, 77 (6): 683-690.