



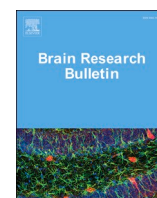
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Editorial

Editorial: Viral infection and brain diseases



The coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has been reported to impact not only respiratory system but also central nervous system (Balcom et al., 2021; Mahalakshmi et al., 2021). COVID-19 patients show a higher proportion of persistent fatigue and cognitive impairment (Ceban et al., 2022). Moreover, while these symptoms arise acutely during the course of infection, increasing lines of evidence suggest the long-term induction of high levels proinflammatory cytokines, cerebrovascular abnormalities, and high risk of neurodegeneration in COVID-19 cases (Heneka et al., 2020; Hernández-Fernández et al., 2020). All these reports attract increasing attention of the potential impacts of virus infection on brain functions. In fact, virus infections of the brain have long been reported to result in either transient or permanent neurological or psychiatric disorders (van den Pol, 2009). Recent studies also hypothesized that the pathogenesis of neurodegenerative diseases including Alzheimer's disease might be relevant to virus infection (Limongi and Baldelli, 2016; Seaks and Wilcock, 2020). However, the exact molecular mechanisms underlying these virus infection-related manifestations are still far from being clearly understood.

This special issue was aimed at publishing high-quality articles covering further exploring the complex interactions between the viral infection and brain disorders, discussing possible underlying mechanisms, characterizing individuals at risk, and providing strategy for the novel preventative or therapeutic approaches. Through rigorous peer review, we have gathered six articles described as follows.

Chronically, in the first paper, Bhagat et al. (2021) demonstrated that Zika Virus (ZIKV) E protein dysregulates microRNA circuitry in neural stem cells (NSCs) and also impairs their proliferative and differentiation abilities through the Wingless/Integrated (WNT) signaling. WNT2 is downregulated in response to ZIKV E protein in human fetal NSCs and one of its molecular targets is microRNA miR-204-5p. These findings provide evidences that miR-204-5p/WNT2 axis is involved in ZIKV induced impairment in the proliferation and immature differentiation of NSCs.

In the article “Mental Health Issues During and After COVID-19 Vaccine Era” (Pandey et al., 2021), the authors briefly summarized the neurological, cognitive, and emotional deficits in COVID-19 patients, including acute neurological symptoms induced by the direct impacts of viral infection leading to cognitive impairment, loss of smell, and brain stroke. Work-associated stress, lockdowns, social distancing, and quarantine in response to contain SARS-CoV-2 also affected the mental health of large populations, regardless of age. Furthermore, the authors also discussed the reasons for vaccine hesitancy and finally analyzed the social determinants of mental health and their impacts on disadvantaged populations during times of crisis. This review article

may help policymakers set up some action plans to mitigate the COVID-19 mental health turmoil during COVID-19 pandemic.

In the third paper, Yang et al. (2021) discussed the possible mechanisms involved in the impacts of COVID-19 infection on central nervous system. The mechanisms may include: 1) direct injury of nerve cells induced by viral invasion, 2) immune activation caused by systemic infection, 3) a high affinity of the SARS-CoV-2 spike protein for neuronal membrane receptors, 4) cerebrovascular disease caused by hypoxia and coagulation dysfunction, and 5) a systemic inflammatory response that promotes cognitive impairment and neurodegeneration. These discussions may provide a framework which benefit to improving patient prognosis and preventing transmission.

Moreover, in another review paper of this special issue, Xie et al. (2022) also summarized the effects and mechanisms of SARS-CoV-2 on the nervous system. The authors indicated that the retro-neural route and gastrointestinal route should be included in the pathways of SARS-CoV-2 invasion. They further indicated that cytokine storm and immune system disorders, hypoxia, ACE2 and renin-angiotensin system, and coagulation abnormalities should be part of the mechanisms of COVID-19 infection-associated neuropsychiatric diseases.

In one systematic review and meta-analysis of this special issue (Cui et al., 2022), four studies were screened from 31,634 participants including 171 COVID-19 positive patients with ischemic stroke. Three of these four articles were retrospective cohort studies and one was prospective cohort study. The analysis revealed that the risk of ischemic stroke was significantly increased in COVID-19 cases. Significant association between the risk of ischemic stroke and COVID-19 was observed in the North America population. These findings may provide direct evidence to support the cerebrovascular abnormalities in COVID-19 patients. More attention should be paid for those risk populations to avoid potential long-term risk of stroke.

Finally, in the sixth paper, Ghassemi et al. (2022) found that rabies virus (RABV) envelop glycoprotein (RVG) infection of hypothalamus and amygdala induces anxiety-like behavior in rats, together with increased corticosterone level, which are mediated by PDZ binding motif (PBM) of RVG. The hypothalamic-pituitary-adrenal axis response to RVG infection of hypothalamus and dorsal hippocampus is dependent to PBM of RVG. These findings indicated that anxiety-related signaling by PBM of RVG seems to be one of the major mechanisms resulting in anxiety behaviors seen in patients with rabies.

In summary, understanding the molecular and cellular mechanisms responsible for the impacts of virus infection on brain functions is mandatory for progress in ameliorating the symptoms or terminating the disease progression. By soliciting articles on current work in the field, we hope this special issue will provide the reader with up-to-date

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resource for deepening the understanding of impacts and the underlying mechanisms of virus-infection on brain function and foster further discussion and future collaboration.

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Song Li^a, Weidong Le^{a,b,c,*}

^a Liaoning Provincial Key Laboratory for Research on the Pathogenic Mechanisms of Neurological Diseases, The First Affiliated Hospital, Dalian Medical University, Dalian, China

^b Institute of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China

^c Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital, Chengdu, China

* Corresponding author at: Liaoning Provincial Key Laboratory for Research on the Pathogenic Mechanisms of Neurological Diseases, The First Affiliated Hospital, Dalian Medical University, Dalian, China.
E-mail address: wdle@sibs.ac.cn (W. Le).