Advances in the study of nervous system infections in COVID-19

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ABSTRACT
Shortly after its outbreak, coronavirus disease 2019 (COVID-19) has very rapidly spread to become a global epidemic. Early clinical findings mainly included typical symptoms such as fever and cough with a very high transmission rate. Recent findings have demonstrated neurological manifestations of atypical symptoms, which is associated with poor prognosis. In this paper, we describe the neurological aspects of COVID-19 pneumonia in terms of relevant neurons, virus-associated receptors, and olfactory and neurological clinical manifestations and offer insights on treatment.

1 Introduction
Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been found to attack the lungs, liver, kidneys, nervous system, immune system, excretory system, and reproductive system and in many cases, results in a new type of pneumonia [1]. More than 35 million cases have been confirmed worldwide until October 2020, with the virus spreading much faster than expected. Most clinical reports of COVID-19 describe typical clinical manifestations such as fever, cough, diarrhea, and fatigue. However, a high level of vigilance should be upheld for
atypical symptoms, such as non-respiratory symptoms, as their correct identification can be effective in reducing the rate of disease transmission and accelerating clinical cure. This article therefore addresses the neurological aspects of COVID-19 infection.

2 Neuronal infection by COVID-19

Novel coronaviruses have the potential to be neuroinvasive [2] and cause adverse effects on neurological function, even severe neurological damage, at onset of infection. SARS-CoV-2 invades the central nervous system (CNS) pathologically, similar to SARS and Middle East respiratory syndrome (MERS) viruses. Novel coronaviruses may enter the CNS via hematogenous or retrograde neuronal pathways [3]. SARS and MERS viruses can cause systemic infection or injury in a wide range of animals and can thus rapidly adapt and cross species barriers to spread or cause pandemics in populations. Such infections can lead to severe clinical signs and high mortality. Neurological damage has been confirmed in SARS and MERS infections, and researchers have found the presence of viral nucleic acids in cerebrospinal fluid and brain tissue during autopsies of patients. Severe infection of the brainstem with SARS coronavirus has been reported in the brains of both human patients and experimental animals. In coronavirus infection in humans, the clinical manifestations described in some studies include respiratory symptoms, myalgia, and fatigue [4–6].

Coronaviruses have viral synapses similar to neuronal synapses that contribute to the rapid infection and immune escape of viruses to nerves [7]. COVID-19 has the potential for direct nerve infection, retention, cross-neuronal transmission, and latency. Nerve damage caused by respiratory coronavirus infection has been recently reported [8–10]. Studies have also shown that in mouse CNS, neurons are the primary targets of infection, causing the degeneration of these essential cells and ultimately, some form of programmed cell death following viral infection [11]. After the initial pulmonary infection and the control of the pandemic, approximately 1/3 of post-infection patients have low antibody titers. Even when the host recovers with treatment, the virus may remain in the neurons for a long time (unlike other cells, most neurons do not regenerate during an entire lifetime) and will reignite when conditions become favorable, which can cause an outbreak to seasonally recur. In a previous study, we found that facial viral herpes can occur rapidly in most patients, starting the day after complete and partial severance of the sensory roots of the trigeminal nerve during neurosurgery [12]. This suggests that viruses from previously infected neurons can persist.

Human coronaviruses are neuroinvasive and neurophilic and have a high affinity for a target molecule that is expressed or abundantly expressed in the posterior horn of the spinal cord in layers I, II, and III, above the brainstem, and up to almost all regions of the brain. This invasion into the nervous system may cause neurological disease. Coronaviruses can be found in the brain or in the cerebrospinal fluid [13]. In severe cases, SARS-CoV-2 may enter the brain through the olfactory nerve in the nasal cavity [14].

A series of studies by showed that PDGF-B (ret/ret) mice underwent increased lung injury after subarachnoid hemorrhage. Given the similar microstructures of the blood–gas and blood–brain barriers and the lung–brain interaction, ependymal cells are possibly involved in neurological and pulmonary
dysfunction caused after subarachnoid hemorrhage. The studies further elaborated on the mechanisms involved in the CyPA signaling pathway [15, 16].

### 3 Association between novel coronavirus-related receptors and the nervous system

Evidence suggests that coronaviruses are not always restricted to infecting the respiratory system. Some patients with COVID-19 have exhibited neurological symptoms such as headache, nausea, and vomiting. Some coronaviruses have been shown to spread from mechanoreceptors and chemoreceptors in the lungs and lower airways to the cardiopulmonary medulla respiratory center via synaptically linked pathways [17]. Although CNS involvement is not a common clinical feature of novel coronavirus pneumonia, the possibility of SARS-CoV-2 entering the CNS remains reasonable. Many viruses occasionally enter the human CNS, even though the majority of diseases they cause do not involve the CNS [18].

Angiotensin-converting enzyme 2 (ACE2), which is widely expressed in the lung, cardiovascular system, intestine, kidney, CNS, and adipose tissue, has been identified as a functional receptor for novel coronaviruses. The expression and distribution of ACE2 suggest that novel coronaviruses may cause some neurological symptoms through direct or indirect mechanisms. ACE2 is a mediator of COVID-19 transmission and acts as a bridge between immunity, inflammation, and cardiovascular disease. Novel coronaviruses differ in several key amino acid residues on their respective receptor-binding domains but have a strong affinity for the human ACE2 receptor, which may explain the greater pathogenicity of SARS-CoV-2 [19].

ACE2 is a key factor in the pathological pathway of neo-coronaviruses, both as a “gateway” to viral invasion and as a key agent of organ damage [20]. The binding of novel coronaviruses to the ACE2 receptor activates the classical renin-angiotensin system regulatory pathway, acting on the lung and extrapulmonary target organs, thereby causing multiple organ injury. The regulation of ACE2 affects multiple pathways and multiple targets [21]. Even the function of its encoding gene, ACE2, is affected by neurological and humoral factors at the overall level [22]. Transmembrane protease serine 2 (TMPRSS2) is another key protein required for cellular neo-coronavirus invasion whose serine protease mechanism is inextricably linked to ACE2 [23]. TMPRSS2 is required to activate the S protein of SARS-CoV-2, which binds to ACE2 in order to enter the host cell. Neurological damage in the acute phase manifests as confusion, dizziness, impaired consciousness, susceptibility to acute stroke, olfactory deficits, memory loss, ataxia, epilepsy, and neuropathic pain [24]. Multiple non-nerve cell types exist in olfactory epithelial cells expressing two host receptors, ACE2 and TMPRSS2, which promote the binding, replication, and accumulation of SARS-CoV-2 proteins. This may be the potential mechanism of olfactory dysfunction often reported in COVID-19 patients. The nasal olfactory epithelium may be the site where the binding force of novel coronaviruses is enhanced [25] and may be a more suitable tissue for detecting SARS-CoV-2 in the early stage before symptoms, even in asymptomatic populations [26].

### 4 Neo-coronavirus infection and olfaction

The loss or decline in the senses of taste and smell can have many causes. In humans, the sense of smell severely affects the sense of taste,
and the two conditions are often jointly affected. Disorders of the olfactory and gustatory systems are usually part of the otolaryngology department, but may actually be caused by neurological damage. To determine the prevalence and assess the diagnostic significance of symptoms of olfactory loss and gustatory loss in neo-coronavirus pneumonia [27]. There is data showing that most patients with olfactory deficit or senile dementia recovered within 3 weeks, with an average recovery time of 7 days for both symptoms. Furthermore, the study found that olfactory deficit and aging appear to be important symptoms and clues for the diagnosis of COVID-19, especially in the early stages of the disease. The possibility that olfactory receptor neurons elicit a rapid immune response in the early stages of disease raises the possibility of neurological infection through olfactory neurons [28]. Recently, the U.S. Centers of Disease Control and Prevention has added the sudden loss of smell and taste to the list of suspicious symptoms for neo-coronavirus infection.

Several types of cells in the nasal cavity are susceptible to SARS-CoV-2. Viral infection results in congestion and edema in the nasal mucosa, thereby impairing or incapacitating the sense of smell. In the absence of other respiratory diseases, the loss of or diminished senses of smell and taste is indicative of possible neo-coronavirus infection [29]. Nasal olfactory epithelial samples may be more suitable than sputum specimens or nasopharyngeal swabs for detecting neo-coronavirus tissue in the stage before the onset of symptoms or even in asymptomatic people. The destruction of taste and smell nerve cells by neo-coronaviruses, which results in the temporary loss of taste and smell in patients, may be a new way of identifying potential asymptomatic infections [30].

5 Main neurological clinical manifestations of neo-coronavirus pneumonia

During the onset of COVID-19, the patient first develops fever and respiratory symptoms [31, 32], followed by muscle soreness, changes in consciousness, and mental symptoms. Neurological examinations of such patients showed positive signs of SARS-CoV-2 infection. Some COVID-19 cases indicate that SARS-CoV-2 can invade the CNS and cause neurological symptoms and signs [33]. Mao et al. [3] analyzed data from 214 laboratory-confirmed COVID-19 patients and observed characteristic neurological manifestations in 78 of them. A comprehensive analysis of the patients’ records for each phenotype, demographic characteristics, medical history, symptoms, clinical signs, laboratory findings, and CT scan of the chest showed three main neurological manifestations: CNS symptoms (vertigo, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy), peripheral nervous system (PNS) symptoms (taste disturbance, manifesting as taste disturbance, olfactory disturbance, visual disturbance, and neuralgia), and musculoskeletal symptoms (skeletal muscle damage). Among the patients with neurological symptoms, 53 cases showed CNS symptoms, 19 cases showed PNS symptoms, and 23 cases showed musculoskeletal symptoms. Neurological involvement was more likely in severely ill patients who were older and more hypertensive but had fewer typical symptoms such as fever and cough. Furthermore, neurological symptoms were significantly more common in severely ill patients, particularly acute cerebrovascular disease, impaired consciousness, and muscle damage. A cohort study conducted by Professor Zhang Dingyu in LANCET showed that middle-aged and elderly patients with hypoalbumi-
nemia and underlying diseases such as hypertension, diabetes, coronary artery disease, and chronic obstructive pulmonary disease were at higher risk for COVID-19. At 6 months after acute infection, the main complaints of COVID-19 survivors were fatigue or muscle weakness, sleep difficulties, and anxiety or depression [34, 35]. Higher D-dimer levels in more severely ill patients compared with those in less severely ill patients may explain why more severely ill patients are more likely to develop cerebrovascular disease. Therefore, neurological manifestations should be monitored for in patients with COVID-19, especially in patients with severe infections and at a high risk of death. These findings offer evidence that neo-coronavirus can infect the nervous, musculoskeletal, and respiratory systems.

In a study by Gutierrez-Ortiz C et al. [36], a 50-year-old male patient who initially presented with cough, headache, low back pain, and fever developed anosmia, right motor nerve palsy, and ataxia five days after the initial visit. Another patient, a 39-year-old male, initially presented with diarrhea and hypothermia and, three days later, presented with dementia and bilateral abducens nerve palsy. The presence of neurological manifestations may be due to an abnormal immune response to COVID-19.

One study showed that 25% of patients with COVID-19 developed CNS manifestations [37]. The neurological manifestations of COVID-19 have not been properly studied; precise, targeted documentation of neurological symptoms in patients, detailed clinical neurological and electrophysiological investigations, attempts to isolate SARS-CoV-2 virus from cerebrospinal fluid, and autopsies of patients may clarify the viral mechanisms involved in these neurological symptoms. Furthermore, the hypercoagulability of COVID-19 patients may lead to a potential high risk of stroke [38]. Patients with pituitary disease who contracted COVID-19 tended to feature hypercortisolism and adrenal depression with Cushing’s disease, adrenal insufficiency with diabetes insipidus and hypothalamic dysfunction, sleep apnea syndrome, and chest wall deformities with acrometropy [39]. The prognosis for neurological involvement is poor. Therefore, in patients with COVID-19, in addition to respiratory symptoms, physicians should pay close attention to neurological manifestations [40–42].

6 Neurological imaging for neo-coronavirus pneumonia

Fernandez et al. proposed acute inflammatory demyelinating polyneuropathy (AIDP) as a common subtype of Guillain–Barre syndrome in patients with COVID-19 [43]. Clinical features of AIDP include numbness and a tingling sensation in the hands and feet, followed by progressive weakness. In general, the prognosis for AIDP is good. Imaging is characterized by high intensity, enlargement, and mild to moderate contrast enhancement of the signal in the cauda equina, nerve roots/plexus, and peripheral nerves. Cauda equina contrast enhancement is the typical MR presentation of Guillain–Barre syndrome. Isolated albumin cells have been observed in the cerebrospinal fluid of most patients with Guillain–Barre syndrome. Immunotherapy (steroids, plasma exchange, or intravenous gamma globulins) may accelerate recovery. Significant residual functional deficits are observed in approximately 15% of patients with Guillain–Barre syndrome [44]. Corrêa et al. reported six confirmed cases of COVID-19 with abnormal cranial nerve lesions on magnetic resonance imaging (MRI)[44]. One patient had bilateral olfactory bulb gadolinium enhancement associated with olfactory loss; one had left optic neuritis; one presented with a right
understanding Barre consistent had neurological imaging The abducens nucleus lesion; two had facial palsy, one unilateral and the other bilateral; and one had bilateral lateral nerve palsy with Guillain–Barre syndrome. The brain MRI of one patient with COVID-19 showed signal changes consistent with viral brain invasion in the cortical region associated with olfaction, the posterior rectus gyrus [45]. The most typical imaging features of acute necrotizing encephalopathy in patients with severe COVID-19 are symmetric, multifocal lesions and invariable thalamic involvement. Other commonly involved sites include the brain stem, white matter, and cerebellum. Computed tomography images showed low attenuation, and MRI T2-weighted fluid-attenuated inversion recovery showed a high signal with internal bleeding. Furthermore, enhanced images can display a contrast enhancement ring [46]. When patients develop transient cerebellar ataxia or disorientation, a reversible splenial lesion (MERS) can be considered as a differential diagnosis for neurological symptoms of COVID-19 [47].

7 Summary

The nervous system is the dominant regulatory and controlling system in the body. Neuronal pathways are monitored and defended quickly and precisely, and the consequences of their disruption, damage, or collapse are insidious and severe. The pathobiological mechanisms of neuroinvasive viruses are still incompletely understood and need to be further investigated. Particularly, the full clinical range of neurological symptoms in COVID-19 patients remains to be discovered and summarized. Thus, understanding the neurological mechanisms of neo-coronavirus pneumonia will vastly improve clinical treatment and help curtail the spread of the disease. Therefore, it is important to explore the neurological impacts of neo-coronavirus infections.

Conflict of interests

Ling He is a staff in Darwin Cell Biotechnology Co. Ltd. We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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