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Review article

The nervous system—A new territory being explored of SARS-CoV-2

Meng Zhang [a,1], Lingyan Zhou [a,1], Jing Wang [b], Kun Wang [a], Yuan Wang [a], Xudong Pan [a], Aijun Ma [a,*]

[a] Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao 266000, China
[b] Department of Rheumatology, The Affiliated Hospital of Qingdao University, Qingdao 266000, China

ARTICLE INFO

ABSTRACT

In December 2019, COVID-19 outbroke in Wuhan, then sweeping the mainland of China and the whole world rapidly. On March 4, Beijing Ditan Hospital confirmed the existence of SARS-CoV-2 in the cerebrospinal fluid by gene sequencing, indicating the neurotropic involvement of SARS-CoV-2. Meanwhile, neurological manifestations in the central nervous system, peripheral nervous system and skeletal muscular were also observed, indicating the potential neuroinvasion of SARS-CoV-2. In particular, we focused on its neurological manifestations and specific pathogenesis, as well as its comparison with other viral respiratory infections. Finally, we further summarized the significance of the neuroinvasion and the follow-up issues that need to be paid attention to by scientists, so as to help neurologists understand the influence of SARS-CoV-2 on nervous system better and promote the accurate diagnosis and efficient treatment of COVID-19.

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1. Introduction

In December 2019, a novel pneumonia of coronavirus, Corona Virus Disease 2019 (COVID-19) outbroke in Wuhan, China, then sweeping the mainland of China and the whole world rapidly, seriously threatening individuals' life and health [1–4]. Due to the high homology with the severe acute respiratory syndrome coronavirus (SARS-CoV), the pathogen was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5].

The main clinical symptoms involved by SARS-CoV-2 is pulmonary manifestations. However, there is growing evidence that SARS-CoV-2 can result in a broad spectrum of neurologic diseases [6–9], which is not surprising, as neurological manifestations have been reported in other respiratory viral infections, including coronavirus, but the nervous system manifestations of COVID-19 are more common and disabling, raising the worldwide concerns about its potential long-term complications to humans [10,11].

In particular, we focused on its neurological manifestations and specific pathogenesis, as well as its comparison with other viral respiratory infections. Finally, we further summarized the significance

of the neuroinvasion and the follow-up issues that need to be paid attention to by scientists, so as to help neurologists understand the influence of SARS-CoV-2 on nervous system better and promote the accurate diagnosis and efficient treatment of COVID-19.

2. SARS-CoV-2

SARS-CoV-2 is a non-segmented, large enveloped, positive single-stranded RNA virus, which is the member of Betacoronavirus genus, with an overall genomic sequence consistency of 96.2% and 79.5% sequence homology with the SARS coronavirus [12]. It has been discovered that SARS-CoV-2 combined with a metalloproteinase, angiotensin-converting enzyme 2 (ACE2) receptors to infect the target cells on their surfaces in line with SARS-CoV, which requires the participation of spike protein(S) and transmembrane protein serine protease 2 (TMPRSS2) [12,13]. Therefore, neurons, endothelial cells, glial cells and arterial smooth muscle cells in the brain, which expressing ACE2 receptors become vulnerable to it [14,15]. Besides, recent researches found that SARS-CoV-2 has a higher affinity for human ACE2 than SARS-CoV [16], which further elucidate the reason for the strong pathogenicity and transmissibility of it.

People are generally susceptible to SARS-CoV-2 [17]. It has shown the aged has higher susceptibility to develop severe sickness, especially with specific comorbidities. Additionally, about

half of the patients infected with SARS-CoV2 had chronic diseases, including cardiocerebrovascular disease as well as diabetes [3].

3. The potential neuroinvasion of SARS-CoV-2

3.1. Initial evidence

A retrospective study [18] showed that among 214 patients diagnosed with COVID-19, more than 30% of them had neurological manifestations. On March 4, Beijing Ditan Hospital confirmed the existence of SARS-CoV-2 in the cerebrospinal fluid by gene sequencing, indicating SARS-CoV-2 could invade the nervous system directly. Moreover, it became the first evidence that SARS-CoV-2 may have the potential neuroinvasion. In fact, the earliest cases of encephalitis/meningitis occurred in Japan [19]. A man in twenties was confirmed as a victim of SARS-CoV-2, who started with fever and fatigue at first, and he was found unconscious at home. During emergency treatment, he suffered from epileptic seizures several times. It was also found SARS-CoV-2 in his cerebrospinal fluid in 8 March, which is the further evidence that the virus is attacking the nervous system.

3.2. Speculated pathogenesis

The central nervous system(CNS) is essential to regulate the whole human body, but it has no immune function against most infections, especially the virus infection. The blood–brain barrier (BBB) is a natural cover for defence, preventing from the intracranial disease of the foreign pathogen. CoVs can enter the CNS from the respiratory tract via hematogenous and transneuronal routes. Increasing evidence shows that a variety of CoVs can not only infect the respiratory system but also have the neurotropism feature [19–24].

The existing researches mainly focus on SARS-CoV. In 2004, the virus RNA was detected in the cerebrospinal fluid of a SARS patient, which led to the scientists' suspicion that SARS-CoV was neuroinvasive [25]. One year later, Xu et al. isolated the virus from the brain tissue of a patient, and the neuropathologic manifestation was nerve cell damage. Meanwhile, the patient showed neurological symptoms, making the hypothesis confirmed [26]. Furthermore, extensive neuronal infections can be observed in animal models.

Furthermore, SARS-CoV entered human cells through a receptor named as angiotensin-converting enzyme 2 (ACE2), which is consistent with SARS-CoV-2 [27]. Therefore, SARS-CoV is neuroinvasive and neurotropic in both animals and humans, which may be related to the development of neurological diseases. Given SARS-CoV2 has similar gene sequencing and pathologic anatomy with SARS-CoV, it could be assumed that SARS-CoV-2 has the same neuroinvasion and pathogenesis.

SARS-CoV-2 might cause a series of neurological damage by two mechanisms; one is the hypoxic brain injury. It is well known that hypoxia, hypercapnia, endocrine and metabolic disorders, and the accumulation of toxic substances caused by respiratory failure in severe COVID-19 patients can cause neuronal swelling and brain edema, leading to brain damage [28]. The other is the parainfectious mechanisms, that is, immune-mediated brain damage. It is mainly referred to cytokine storm [29]. Cytokine storm syndrome is a highly inflammatory state characterized by sharply elevated cytokine levels, overshooting immune responses and explosive multi-organ failure, leading to vasodilatory dysfunction, membrane leakage, coagulation dysfunction, multiple organ failure, and severe vasospasm shocks. Besides, if ECMO is used, the contact between fluids in vivo and circuits in vitro might activate clotting and inflammatory pathways, leading to disseminated intravascular coagulation in severe cases [30,31].

3.3. Significance of neuroinvasion

Firstly, given that SARS-CoV-2 has the underlying neuroinvasion, carrying out the therapy to resist it as soon as possible can block the entry of the virus to the CNS. Moreover, the ability of antiviral agents to cross the blood–brain barrier is also an issue to consider in the future. Although the progression of new antiviral drugs requires a lot of workforce and material resources, it can not benefit the general public a lot in the current epidemic. However, as the outbreak fades, the virus may mutate into a coronavirus, which is similar to the influenza virus, spreading from person to person over the long term. Therefore, it is necessary to accelerate the research and development of specific antivirus drugs and vaccines steadily.

Secondly, considering that SARS-CoV2 might be latent in some neurons to get away with immune surveillance, we can not guarantee that the virus has been eliminated. Actually, SARS-CoV-2 is still can be detected; even the COVID-19 patients are under the convalescent period [32]. If existing in the nervous system for the long term, it is likely to serve as a trigger for some human neurological diseases in those genetically predisposed individuals. Thus the long-term follow-up of patients is an essential task in the future.

Thirdly, the blood-brain barrier degrades gradually with age, which indicates that the nerve invasion ability of the virus to the elderly increases. Once the virus invades the nervous system, demyelination, cell apoptosis and neurodegeneration will occur, then further aggravating the brain ageing and neurodegenerative diseases [33]. Neurologists will face more age-related neurodegenerative diseases after we control the outbreak. Therefore, more long-term neurological follow-up of the elderly is needed after SARS-COV-2 infection.

The final concern is the immuno-therapies for COVID-19 with autoimmune diseases of the nervous system. Once diagnosed, neurologists must assess the risks and benefits of immunotherapy in light of the different conditions of the disease. For example, high doses or long-term use of steroid hormones may put patients at further risk for COVID-19 infection. Protective immunoglobulin is recommended if possible. Additionally, given that the crucial step to control the pandemic is the application of SARS-COV-2 vaccination, it is indispensable to weigh the safety and effectiveness of vaccination during immunotherapy.

4. Neurological manifestations of COVID-19

An increasing number of evidence indicated that SARS-CoV-2 might have potential neuroinvasion, hence we summarized the existing related researches and data of COVID-19, the neurological signs of it could be divided into three categories:symptoms involving the central nervous system, peripheral nervous system, and skeletal, muscular symptoms.

4.1. Central nervous system (CNS) diseases or symptoms

4.1.1. Acute cerebrovascular diseases

The virus infections can cause vascular endothelial injury and vascular system damage, then leading to ischemic and hemorrhagic infarcts through overactive inflammation response, thrombosis and vasculitis [34,35].

A retrospective case series study in Wuhan, China [18], showed that the severe patients of COVID-19 commonly had acute cere-

brovascular diseases, and the pathophysiological changes during the infection may render the victims prone to it.

Firstly, in the latest study, 52% of patients of COVID-19 had elevated Il-6 levels, and 86% of them had elevated CRP(3), suggesting a significant inflammatory response in their bodies. Meanwhile, inflammation is also essential in the occurrence, development as well as prognosis of cerebrovascular diseases and may trigger cerebrovascular events [36]. Secondly, according to the laboratory examination of the severe patients who had coagulation dysfunction and elevated D-dimer [37], those people may have more possibility of venous thrombosis and hemorrhagic stroke [38]. A 75-year-old woman infected by SARS-CoV-2 without any predisposing factors suffered from severe bilateral pneumonia and acute pulmonary embolism, suggesting the severe infections is a precipitant factor of acute venous embolism and stroke [40,41].

Thirdly, SARS-CoV-2 readily attacks the lung, then causes dyspnea and decreased blood oxygen saturation [3]. Hypoxemia attributes the alteration of consciousness, confusion or delirium, causing an acute or subacute stroke or intracerebral hemorrhage [41,42]. Additionally, overexpression of ACE2 reduces the risk of ischemic stroke, which explains the reason why elderly COVID-19 patients are more likely to have a stroke [43,44].

4.1.2. Viral encephalitis and meningitis

Although the virus seems to have a hard time penetrating the central nervous system, pathogens can be abnormally active in spreading and replicating, then may induce overreacting immune response and lead to fatal meningitis and encephalitis. The discovery of the positive RT-PCR of CSF [19] suggested that meningitis and encephalitis may associated with viral invasion of the CNS. Elevated temperature, headache, vomiting, and consciousness disorders are common signs, which are similar to acute encephalitis [45]. Autopsy reports also showed that there was the edema of brain tissue and degeneration in the neurons of those victims [20]. Presumably, SARS-CoV-2 may enter the CNS from the respiratory tract via hematogenous and transneuronal routes like other CoVs [46].

4.1.3. Acute hemorrhagic necrotizing Encephalopathy/Acute disseminated encephalomyelitis

Acute necrotizing encephalopathy is a rare acute and severe explosive encephalopathy, which usually occurs after a viral infection. The most common hypothesis for its pathogenesis is the destruction of the blood–brain barrier caused by cytokine storm [27], which is also the possible pathogenesis of COVID-19 [47]. Neo Poyiadji et al. reported the first case of acute necrotizing hemorrhagic encephalopathy associated with COVID-19 from a woman in her fifties. For the first three days, her symptoms were fever, cough and altered mental state. Laboratory tests confirmed the SARS-CoV-2 infection and neuroimaging showed characteristic changes: symmetrical multifocal changes and thalamic invasion [48]. Reichard et al also found pathological findings which are similar to acute disseminated encephalomyelitis in a patient who died from complications of COVID-19 [49]. However, whether the neuropathological lesions resulted from primary vascular disease secondary to white matter damage or demyelination disease caused via a parainfectious mechanism.

4.1.4. Leukoencephalopathy

Radmanesh et al. observed two kinds of imaging characteristics by cerebral MRI in 11 patients with severe COVID-19: diffuse leukoencephalopathy and microhemorrhages, speculating that they were late complications in severe COVID-19 patients [50]. Given that similar involvement patterns have been described in patients after anoxic injury, it was considered delayed post hypoxic leukoencephalopathy (DPHL) which was associated with oligoden-

drocyte damage and demyelination [51,52]. Besides, Sachs et al also reported a COVID-19 patient who sufferred from leukoencephalopathy with microhemorrhage. It is a 59-year-old man who was hospitalized for upper respiratory symptoms and fever. Brain MRI mainly showed large posterior fused white matter lesions, significant microhemorrhage in the corpus callosum and high posterior circulation perfusion [53], which could also be seen in acute disseminated encephalomyelitis, acute hemorrhagic encephalomyelitis, vasculitides and posterior reversible encephalopathy syndrome [54,55]. Recently, Franceschi et al describe 2 COVID-19 patients whose brain imaging suggested hemorrhagic posterior reversible encephalopathy syndrome [56]. The authors summarized three mechanisms of PRES: cytokine release syndrome which breaks down the BBB; hypoxia caused by inflammation; unstable blood pressure [57,58].

4.1.5. Acute myelitis

A 66-year-old male in Wuhan was diagnosed as COVID-19 with acute myelitis [59], presenting with fever, pain, and acute delayed paralysis of the lower extremities along with urinary and fecal incontinence. The patients responded well to immunoglobulin and hormone. Meanwhile, the high levels of C-reactive protein, inflammatory cytokines, and serum ferritin suggested that his myelitis was a result of a cytokine storm.

4.1.6. Others

There are also other central nervous system manifestations reported [18] such as headache, dizziness, ataxia, impaired consciousness, and epilepsy. Dizziness and headache are the most common complaints. A headache expert pointed out that there are two stages of COVID-19-related headache. The first stage is an acute headache caused by a viral infection, primary cough, tension-type and heterophoria. The headache in the second stage (bounded by 7–10 days) could attribute to hypoxia, which could be used as a predictor of cytokine storm onset [60]. In the patients who had severe virus infection also showed agitation, corticospinal tract signs as well as a dysexecutive syndrome [61]. A COVID-19 patient with meningitis/encephalitis also developed epilepsy [19], and another present as focal status epilepticus as the first symptom [62]. Therefore, it is reasonable to speculate that COVID-19 patients may develop epilepsy under conditions of hypoxia, endocrine and metabolic disorders, and multiple organ damage.

In addition, anosmia may occur before the symptoms of viral infection. It has been reported that CoVs can enter the CNS in the early stages of infection through the olfactory nerve [63], which indicates the same transneuronal routes of SARS-CoV-2. A multicenter study in European [64] found olfactory disorder in patients who did not need intensive cares. And the impaired functions do not always recover as the disappearance of the typical infection symptoms. Meanwhile, compared to the work of MAO et al.in Wuhan, China, the prevalence of the dysfunctions was significantly higher in European. Considering the different affinity of SARS-CoV-2 to different populations and the diversity of ACE2 expression [65], studies should focus more on the polymorphisms of ACE2 in different races.

4.2. Peripheral nervous system (PNS) symptoms

4.2.1. Guillain-Barré syndrome

Guillain-Barrésyndrome is a kind of neuroimmune disease secondary to respiratory or gastrointestinal infections. It is known that there is a molecular imitation mechanism. The invading virus has similar epitopes with some components of the nervous system, stimulating the immune system to produce antibodies which can not only bind to the virus, but also cross-react with components

of the nervous system, then causing a series of neurological dysfunction [66].

The first Guillain-Barré syndrome associated with COVID-19 case was found in Wuhan, China [68]. A 61-year-old woman suddenly developed progressive lower limb weakness without fever or cough. Three days later, her condition worsened, and the weakness spread to the upper limbs. Typical blood and cerebrospinal fluid test and nerve conduction have confirmed the presence of Guillain-Barré syndrome. On the eighth day, she started to have the characteristic fever, cough, and chest CT findings of COVID-19. Laboratory tests confirmed the SARS-CoV-2 infection. Then the northern Italy hospitals reported similar cases, involving motor and sensory disorders of the limbs as well as ataxia [67]. Jessica et al reported a COVID-19 patient admitted to hospital with an abnormal gait. Although the neurologist did not observe ophthalmoplegia, in consideration of her excellent response to immunoglobulin, apparent ataxia and hypoxia of the lower extremities, she was eventually diagnosed as Miller–Fisher-like syndrome overlapping with COVID-19 infection [69]. Consider that these are all observational studies, more epidemiological evidence is needed to support the potential relationship between Guillain-Barré syndrome and COVID-19 in the future.

4.2.2. Others

Hyposmia is also a common symptom in COVID-19 patients. Acute respiratory symptoms associated with coronavirus are characterized by hypoxia, one of the ways that coronavirus associated with the nervous system, causing endocrine and metabolic disorders, edema in the brain and subsequent neurological manifestations. Besides, taste, vision impairment, and facial pain have also been reported [44].

4.3. Skeletal muscular symptoms

Skeletal muscular symptoms were also reported in COVID-19 patients [18]. Given the high levels of lactate dehydrogenase and creatine kinase, it is speculated that the symptoms resulted from skeletal muscle injury which might be associated with ACE2 existing in it [44]. Nevertheless, whether SARS-CoV-2 damages skeletal muscle through the receptor on the cells still needs further researches. Moreover, the elevated pro-inflammatory cytokines, which indicated abnormal immune response mediated by infection, might be another reason for it.

5. Comparison with other viral respiratory infections

A great many viral infections could cause varying degrees of damage to the nervous system, including its the structure and function. Such as acute disseminated encephalomyelitis, toxic encephalopathy and severe acute demyelinating diseases in connection with the post-infectious inflammatory response. The presence of the virus in cerebrospinal fluid also confirms the nerve invasiveness of the virus [70,71]. As SARS-COV-2 has stronger binding ability to ACE2, it is more pathogenic and transmissible as well as debilitating than SARS-CoV and MERS-CoV [72]. At the same time, COVID-19 and acute respiratory distress syndrome patients had twice the rate of thrombosis complications compared to the ARDS from other causes, which explains why the rates of COVID-19 associated d-dimer elevation and concurrent stroke appear to be much higher than other viruses. Therefore, timely anticoagulant therapy is essential for the prognosis of patients [73].

6. Conclusion

In conclusion, SARS-CoV-2 has potential neuroinvasion and may cause a series of nervous system diseases or symptoms. Once involving the nervous system, it usually predicts poor prognosis. Therefore, patient with COVID-19 requires more physicians'attention to evaluate their neurologic manifestations as early as possible. Paying attention to the patients who have neurological symptoms as the first manifestation other than the typical cough, vomiting, diarrhea, and fever is imperative for the control of the rapidly evolving epidemic. Gene sequencing of cerebrospinal fluid and other neuroimaging examinations should also be taken in necessity.

7. Fundings

No funding.

8. Ethics approval

This study was based on publicly available data and did not require ethical approval.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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