Review Article

Covid-19 and Neurology

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Abstract

The coronavirus 2019 (COVID-19) infection initially affects the respiratory system. However, nervous system involvement lately becomes a significant feature of COVID-19 infection. The neurologic manifestations can be direct and indirect viral effects or just the non-specific complications from critical illness. The prevalence of stroke in patients with COVID-19 is higher than in other viral infections. COVID-19 patients with stroke have a high mortality rate. Central nervous system involvement with alteration of consciousness commonly occurs in hospitalized patients with COVID-19. As well as any other viruses, COVID-19 infection may likely be antecedent to Guillain Barre Syndrome. COVID-19 vaccination may cause neurological complications.

Keywords: COVID-19, Coronavirus 2019, SARS-CoV-2, Neurologic disease, Neurology

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Introduction

The coronavirus 2019 (COVID-19) significant feature with a respiratory illness confers its initial name as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The lungs are the initial organs of damage by COVID-19. The virus binds to angiotensin-converting enzyme receptor-2 (ACE 2), which is abundantly found in the lungs, then reduces its function. ACE 2 cannot convert angiotensin-2 (AGE-2) protein, leading to AGE-2 protein accumulation, induced inflammatory, prothrombotic, and immune-mediated activity.

In the early stage of the pandemic, associated neurologic disorders were not much aware. However, neurologic involvements have lately become the central topic of interest. The significant neurologic presentations of COVID-19 patients include anosmia (loss of smell) and ageusia (loss of taste).[1] The neurologic complications during and after COVID-19 infection are common and lead to higher mortality risk. These tragic neurologic complications occur in either nonsevere or severely ill patients.[2] Nowadays, Neurologists play a significant role in the multidisciplinary team approach for COVID-19 treatment.

The author searches the Pubmed, MEDLINE, and Google Scholar for COVID-19 and neurology using the term "COVID-19" or "coronavirus 2019" or "SARS-CoV-2" and "neurology" or "stroke" or "neurologic disease" or "central nervous system" or "peripheralnervous system".

Results

COVID-19 and Stroke

Since the beginning of the COVID-19 outbreak in Wuhan, mainland China, stroke has become a significantly associated disease.[3] Patients with severe viral infection are initially the high-risk group for stroke.[4] The stroke rate of 1.6% in patients with COVID-19 is almost eight times higher than in influenza.[5] Not only stroke but also other vascular diseases are associated with COVID-19.[6] However, the American Heart Association (AHA)'s COVID-19 Cardiovascular Disease Registry, including about 20,000 adults hospitalized with COVID-19 between March and November 2020 in the United States, reported a total rate of an ischemic stroke coming down to 0.75%. Although it becomes lower than the previous estimation, it is still higher than in influenza.[7] The most recent international study, including more than 100,000 patients hospitalized with COVID-19 in 457 stroke centers from 70 countries, reported a 1.48% stroke rate.[8]

Several mechanisms are responsible for thromboembolism in patients with COVID-19 infection.[4] Elevated C-reactive protein, D-dimer, and ferritin during the stroke episode in severe COVID-19 infection suggest the prothrombotic state's existence.[9, 10] The hyper-coagulable state followed COVID-19 infection leading to cerebral venous thrombosis was reported.[11] The onset of stroke during the active COVID-19 infection supports the concept of para-infectious immune-mediated mechanism. However, the post-infectious immune-mediated mechanism may play a significant role in some patients who have a stroke after subsiding COVID-19 infection. Direct endothelial cell infection with COVID-19 causing an angiopathic cerebral infarct was reported in post-mortem autopsy.[12] The viral fragment can be found in the capillary endothelium of the brain.[13] The postulated mechanisms of thromboembolism associated with COVID-19 infection are shown in Table 1. However, the exact mechanism for thromboembolic events, including stroke, is still controversial.

Table 1 The postulated mechanisms of thromboembolisms due to COVID-19 infection

	The postulated mechanisms of thromboembolisms due to COVID-19 infection
1.	Induced hypercoagulable state
2.	Para-infectious immune-mediated
3.	Post-infectious immune-mediated
4.	Direct endothelial cell infection

A stroke occurs in patients with symptomatic COVID-19 infection rather than asymptomatic ones. COVID-19 patients with stroke have an almost 50% mortality rate. The AHA's COVID-19 Cardiovascular Disease Registry reported that patients who had an ischemic stroke during hospitalization for COVID-19 had double the probability of death than those who did not have a stroke.[7] The mortality rate is even elevated in patients with multiple vascular risk factors. Most of the death cases are associated with severe COVID-19 infection.[14] Due to the neurological examination and investigation limitation in severe COVID-19 infection, the rare venous stroke and the typical cerebral infarct become challenging to diagnose. The high degree of suspicions would help neurologists to be aware of associated stroke in COVID-19 infection.

The COVID-19 pandemic also impacts overall stroke services. Delayed arrival is more often during the pandemic period.[15] In the usual period, the delayed arrival of stroke patients is due mainly to low recognition of prompted treatment-seeking.[16] In contrast, during the pandemic period, the delayed arrival is related to the hospital's fear of infection.[15] The admission with stroke is lower during the pandemic than the average period.[17,18] This decline in stroke admission occurred worldwide.[8] The overall clinical outcomes look worse than those of the standard period.[15]

Central nervous system (CNS) involvement

Almost one-third of COVID-19 patients have an alteration of consciousness during admission.[12] However, COVID-19 associated encephalitis is uncommon. Less than 1% of COVID-19 patients with neurologic involvements have encephalitis.[4] The most common form of CNS involvement of COVID-19 infection is hypoxic encephalopathy due to severe respiratory failure.[19] The diagnosis of encephalitis in patients with COVID-19 is according to the consensus of the International Encephalitis Consortium. The statement consensus includes the presentation of mental status changes (defined as declined or altered level of consciousness, drowsiness, or behavioral changes) lasting more than 24 hours and the presence of two or more of the following criteria: 1) generalized or partial seizures not entirely attributable to preexisting epilepsy 2) new onset of focal neurologic features 3) cerebrospinal fluid (CSF) white blood cell count more than five per cubic millimeter 4) abnormality of cortical parenchyma on neuroimaging suggestive of encephalitis that was either new from prior studies or appears acute in onset 5) abnormality on electroencephalography (EEG) consistent with encephalitis and not attributable to another etiology.[20]

However, more than half of COVID-19 associated encephalitis patients have normal magnetic resonance imaging (MRI) of the brain.[21] Moreover, only three cases report direct evidence of the COVID-19 virus in the CNS so far.[22-24] There was no evidence of encephalitis in 606 hospitalized patients with COVID-19 in New York who had neurologic manifestations.[25] A rare CNS manifestation such as a new-onset refractory status epilepticus without a newly developed lesion in the brain but positive reverse transcription-polymerase chain reaction (RT-PCR) COVID-19 was reported.[26]

Peripheral nervous system (PNS) involvement

Anosmia and ageusia are distinctive PNS manifestations in non-hospitalized COVID-19 patients. Guillain Barre Syndrome (GBS) is a post-infectious, immune-mediated polyneuropathy after a particular viral or bacterial infection, such as *Campylobacter jejuni,* Zika, and influenza virus. COVID-19 infection can likely be preceding to GBS. The first case of GBS-associated COVID-19 infection from Wuhan, China, was reported by Zhou et al. in April 2020.[27] Then, few more cases of GBS-associated COVID-19 infection came out worldwide. Two Miller Fisher Syndrome cases, a GBS variant, were reported by Gutierrez-Ortiz et al. in late April 2020.[28] The intravenous immunoglobulin (IVIG) and plasmapheresis, the standard treatments for GBS, remain the recommended therapy for GBS-associated COVID-19.

The para- and post-infectious autonomic dysfunction may exist from the beginning of the acute phase to 4 months later of COVID-19 infection. The typical clinical manifestations include but are not limited to orthostatic symptoms without tachycardia or hypotension, postural tachycardia syndrome (POTS), and sudomotor dysfunction. All clinical features are usually mild and sometimes asymptomatic. It is essential for neurologists to aware of the autonomic dysfunction associated with COVID-19 infection to avoid missing diagnosis.[29]

There have been three cases of myasthenia gravis (MG) in COVID-19 infection reported so far. Likely, MG was subclinical and became unmasked by the critical illness or treatment, not the virus's direct effect on the neuromuscular junction.[30] Besides muscular involvement in COVID-19 infection, myopathy is usually due to critical illness, not the virus's direct effect on the muscle.

Discussion

When the neurologic manifestations occur in patients with COVID-19 infection, we need to define whether they are direct and indirect viral effects or just the non-specific complications from critical illness. From the evidence we have had so far, the non-specific nervous complications are far more common than the direct and indirect viral effects.[25,31] The neurologic manifestations in COVID-19 infection are shown in Figure 1.

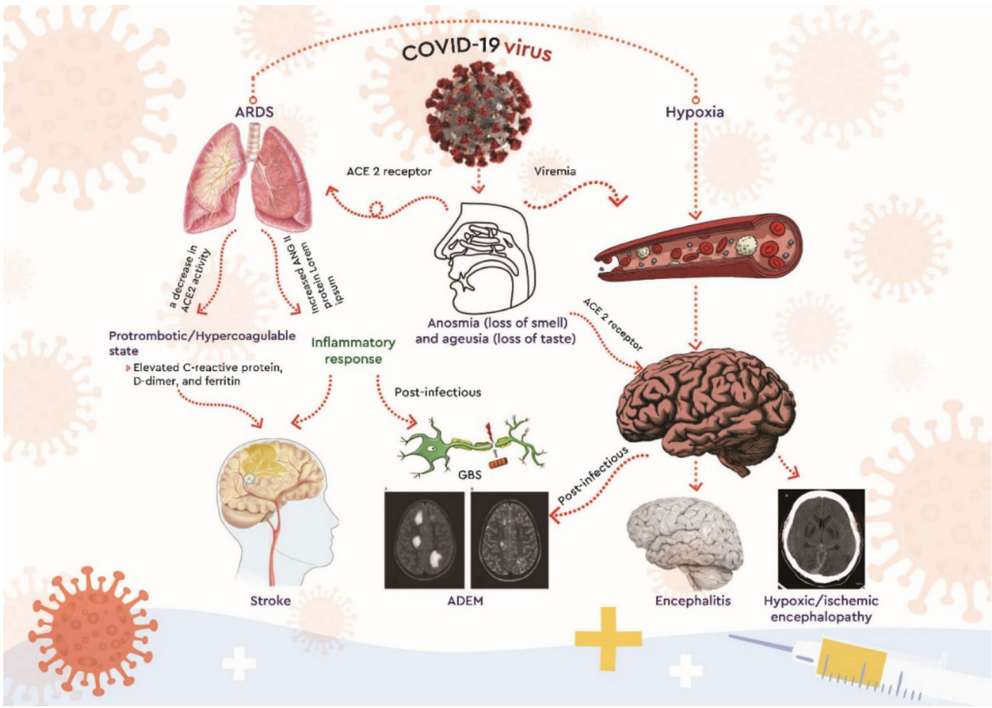

Figure 1 The neurologic manifestations in COVID-19 infection.

The long-term effect of COVID-19 on the risk of stroke is unknown. The story of sequelae after the viral outbreak tells us to be aware of the long-term global effect.[32] According to the evidence of permanent damage in the lung causing by COVID-19, it is very likely that the vascular system's catastrophes remain long after subsiding of infection. The long-term neurological complications associated with COVID-19 seem to be diverse and still need to be monitored.

At the time of writing this review, the vaccination program for COVID-19 has just launched in some countries. There was no significant neurologic adverse reaction reported in the phase 2 vaccination trial.[33] However, post-vaccination neurologic adverse reactions, such as Bell's palsy or Guillain Barre Syndrome, need to be monitored.

Five cases of venous thrombosis and thrombocytopenia after COVID-19 vaccination were reported in some European countries.[34] The European Medicines Agency (EMA) recently recommended that physicians be aware of possible thromboembolism cases like cerebral venous sinus thrombosis, pulmonary embolus, and deep vein thrombosis in people who received the Astra Zeneca/Oxford (ChAdOx1 nCoV-19) vaccine.[35] The preprint report from Oxford University demonstrated that AstraZeneca's COVID-19

Vaccine benefit is greater than the risk of thrombo-embolism.[36] Six cases of central venous thrombosis and thrombo-cytopenia in the first two weeks after administering the Johnson & Johnson (AD26 nCoV-19) COVID-19 vaccine were reported in the United States. Both ChAdOx1 and AD26 vaccines use an adenovirus to transport genetic instructions for making the COVID-19 spike protein into human cells. It is postulated that adenovirus may bind to platelets and causes platelet pre-activation leading to a prothrombotic state and thrombocytopenia.[37]

The public influence effect by widely using social media may intensify rumors about the nonsense adverse reactions related to COVID-19 immunization. The immunization stress-related response (ISRR) describes the spectrum of clinical manifestations after a vaccine injection, including acute stress responses, vasovagal reactions, and dissociative neurological symptom reactions (DNSRs).[38] ISRR can cause immunization delays and refusals if not well managed.[39]

The collaterally neuro-psychological impacts may be significant and common in patients with COVID-19.[40] We have not included neuropsychological manifestation in this review as yet. One lesson learned from the Middle East Respiratory Syndrome Corona Virus (MERS-CoV) outbreaks is the long-term psychological impacts.[41] We believe the long-term psychological impact after the COVID-19 pandemic should also be huge.

Study limitation

The rapid nature of the COVID-19 pandemic limits the methods used for the studies included in the review. Lacking long-term following up data leads to the limitation of the outcomes evaluation. Most of the studies included in this review are limited to just a case report, case series, retrospective type, or correspondence. Only one prospective study is included in this review. The publication of COVID-19 articles becomes raging torrents. More than 100,000 articles about COVID-19 have come out so far. This review may become outdated fast.

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