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Review Article

Neurological manifestations in COVID-19 infection

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ABSTRACT

The emerge of coronavirus disease 2019 (COVID-19), previously known as novel coronavirus (2019-nCoV), in Wuhan, China, in December 2019, has spread throughout the world. COVID-19 is known to cause respiratory disease. However, several scientific studies have shown nervous system involvement in COVID-19 infection. The potential mechanisms of this infectious disease transmission to the brain are through infected olfactory epithelium, hematogenous spread and immune-related pathway. Nervous system involvement in COVID-19 infection can be classified as central nervous system (CNS) involvement, peripheral nervous system involvement (PNS) and muscle. CNS involvement, including headache, cerebrovascular disease, impaired consciousness, meningitis, encephalitis, dizziness and seizure. PNS manifestations, such as anosmia, ageusia or dysgeusia, oculomotor nerve palsy and Guillain-Barre syndrome (GBS). Myalgia or arthralgia is the most common presentation of muscle involvement in COVID-19 infection. This review concludes that neurological disorders as COVID-19 clinical features must be recognized by medical professionals in order to have appropriate diagnosis and treatment so that COVID-19 patients can have better prognosis.

Keywords: Coronavirus disease, COVID-19, Neurological manifestation, Neurology

INTRODUCTION

In December 2019, it was found a large outbreak of viral pneumonia, caused by a novel coronavirus (2019-nCov) in Wuhan, China. This new coronavirus was officially named by World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) on 11 February 2020. Due to the alarming levels of spreading and severity, WHO declared COVID-19 as pandemic on 11 March 2020.[1]

The emergence of this new pathogenic virus has become the third most contagious disease in human population in the twenty-first century since severe acute respiratory syndrome coronavirus (SARS-Cov) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.[2]

WHO has reported a cumulative total of nearly 26 million confirmed cases and 850,000 deaths as of 01 September 2020.[3]

COVID-19 mainly manifests as an acute respiratory infection, characterized as pneumonia. However, there is evidence indicating neurological manifestations ranging from headache to encephalitis.[4] Because of the diverse symptoms in COVID-19 infection, they may cause misdiagnose in clinical practice which may lead to inappropriate treatment of COVID-19 patients with presenting non-specific neurological symptom initially. This review aims to evaluate the cases, which outline the involvement of human nervous system in COVID-19 infection.

REVIEW OF LITERATURE

COVID-19

Coronaviruses are members of *Coronaviridae* family. There are four main subgroups of coronaviruses, which are *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. Both *Alphacoronavirus* and

Betacoronavirus usually infect mammals. Both *Gammacoronavirus* and *Deltacoronavirus* mostly infect birds.[5]

COVID-19 is a *Betacoronavirus*, enveloped, pleomorphic or spherical particles, 60 to 140 nm in diameter, single stranded ribonucleic acid (RNA), unsegmented, nucleoprotein capsid, matrix and S protein, which can infect both humans and animals.[5,6] The ultimate viral proteins are nucleocapsid protein, membrane glycoprotein and spike glycoprotein. The difference of COVID-19 from other coronaviruses is an additional glycoprotein which has acetyl esterase and hemagglutination properties.[7]

The envelope spike protein of the COVID-19 recognizes human angiotensin-converting enzyme II (ACE2) as entry receptor and mostly infects lung epithelial cells. The receptor binding area of the spike protein attaches onto the ACE2 receptor and then, the host serine transmembrane proteases 2 (TMPRSS2) splits the spike protein to exhibit fusion peptides capable to fuse the viral and cell membranes. ACE2 is found in many human tissues. Therefore, infection in COVID-19 can show various symptoms depending on which tissues are infected. Most common COVID-19 symptoms are fever, cough, and fatigue. However, there are also other symptoms which have been observed, such as headache and anosmia. These demonstrate that COVID-19 can involve other human organs, such as neurology.[5]

Potential mechanism of nervous system involvement

Although various evidences have shown the involvement of nervous system in coronavirus infection, it remains complicated to explain how the different neurological manifestations relate to the pathophysiology of COVID-19 infection. It is also difficult to determine whether the manifestations result from directly or indirectly viral infection.[8]

One of the possible mechanisms of COVID-19 directly infection to the brain tissue is via the infection of the olfactory epithelium and transmission to the subarachnoid space through cribriform plate.[9] This corresponding effect shows the interaction of ACE2 receptors with spike protein of TMPRSS2 in olfactory region and promote neurodegeneration. This mechanism supports the present of anosmia and hyposmia as key features in COVID-19 patient.[8]

ACE2 receptors are found on glial tissues, neurons and brains vasculature which provide a target for the entry of COVID-19. The role of blood-brain-barrier in preventing this virus infection remains unclear. The presence of the virus in circulation provides an entry route into cerebral bloodstream and the viral spike protein can interact with ACE2 receptors in capillaries endothelium in micro vessels where the blood movement is slow. This leads to viral evolving from capillaries endothelium and harm the blood vessels and neurons. As ACE2 is cardio-cerebral vascular protecting factor, its impairment may cause a leak of the virus in the brain. The damage blood vessel via unknown mechanism may also cause intracerebral hemorrhage which can have fatal consequences in COVID-19 patients.[4]

The other proposed mechanism is via an immune-related pathway. Cytokine storm is an over-activation of the immune system caused by the infection, which results in huge accumulation of inflammatory substance, leading to multiple organ failure and respiratory distress. This may play an important role in increasing mortality rate in critically ill COVID-19 patients. Cytokines, include interferon (IFN), interleukin (IL), chemokines, colony stimulating factor (CSF) and tumor necrosis factor (TNF), are produced by immune cells. Low levels of T cell, both cluster of differentiation T-lymphocyte cell CD4+T and CD8+T, and high levels of both IL-6 and IL-10 are found in severely ill patients. Therefore, T cell and cytokines are positively corresponding with the severity of COVID-19 patients.[10]

Neurological manifestations

Although COVID-19 mostly manifests as pneumonia, there are growing evidences shown that it also affects nervous system, including central nervous system (CNS), peripheral nervous system (PNS) and muscle.[11] A study of 214 patients of COVID-19 infection, which was conducted in Wuhan, China, showed that 36.4% patients had nervous system manifestations with 24.8%, 8.9% and 10.7% present CNS, PNS and skeletal muscle injury symptoms, respectively. It was also reported that neurological disorders were more common in severely ill patients than in non-severe ill patients (45.5% versus 30.2%). The severity of the COVID-19 is defined by using the American society guidelines for community-acquired pneumonia.[12]

Central nervous system

Headache

Headache is reported as one of the common symptoms of COVID-19. A previous research in China (1099 hospitalized COVID-19 patients) demonstrated that 13.6% of the patients had headache, with 15% in severely ill patients and 13.4% in non-severe ill patients.13 34% of the retrospective case series of 62 patients admitted to hospital with laboratory confirmed COVID-19 infection in Zhejiang Province, China, also had headache.[14] Another study (24 patients) in Washington, showed that 8% patients complained headache as one of the COVID-19 symptoms.[15]

However, the characteristic of the headache in COVID-19 infection requires further studies. A case series of 13 patients confirm COVID-19 infection described headache as moderate to severe intensity and locating in bilateral frontal and temporal areas. Nine patients who took

Paracetamol or NSAIDs (non-steroid anti-inflammatory drugs) reported partially response or temporary recovery lasting hours.[16]

Cerebrovascular disease

The risk for arterial and venous thromboembolism associated with inflammation, hypoxia and diffuse intravascular coagulation may be higher in COVID-19.[11] Mostly patients with cerebrovascular disease were more prevalent in severe ill patients and having cardiovascular risk factor, including hypertension, diabetes and previous history of cerebrovascular disease.[17]

The possible mechanisms of developing cerebrovascular disease in COVID-19 are hypercoagulability which has been named as sepsis-induced coagulopathy and depletion in ACE2. These may result in tissue damage. In addition, cytokine storm in COVID-19 leads to ischemic brain damage and enhances the risk of intracranial bleeding.[10,18]

Mao et al presented that 2.8% of COVID-19 patients had cerebrovascular disease, which 5.7% of those were found in critically ill patients and 0.8% in non-critically ill patients. It was found that ischemic stroke was more common than hemorrhagic stroke. The onset of the symptom to hospital admission was reported between the first to the eighteenth day.[12]

A retrospective study of 219 COVID-19 patients in Wuhan, China, showed that 5% of the patients developed new onset of cerebrovascular disease with 90.9% of those patients had ischemic stroke and 9.1% suffered hemorrhagic stroke. It also reported that the cerebrovascular disease was more likely to be in severe patients.[19]

Impaired consciousness

Impaired consciousness is one of the symptoms of COVID-19 which is more likely in severe patients. 69% of 58 patients who admitted to hospital in Strasbourg, France, because of acute respiratory distress syndrome due to COVID-19 had impaired consciousness.[20] A systematic review study presented that impaired consciousness was found in 5.1% of COVID-19 patients. It was more frequently in severe patients.[9] Another research in China also reported that 7.5% of COVID-19 patients had impaired consciousness. 14.8% and 2.4% of those patients were in severe and non-severe disease, respectively.[12]

Meningitis/encephalitis

There are limited studies about meningitis or encephalitis associated with COVID-19 in cerebrospinal fluid (CSF) or brain. However, there were found few cases of meningitis or encephalitis in COVID-19 infection. The first case of COVID-19 associated with meningitis or encephalitis was observed in Japan. A 24-year-old man admitted to the hospital with history of fever, headache, generalized weakness, sore throat, impaired consciousness, neck stiffness and seizure. Head computed topography (CT) scan ruled out brain edema. Chest CT scan showed small ground glass opacity on the right superior lobe and both sides of inferior lobe. COVID-19 was not detected in nasopharyngeal swab, but surprisingly it was found in CSF. Contrast-enhanced imaging demonstrated right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus.[21]

A case report in United Kingdom presented a 22-year-old woman with 3-week history of fever, headache, neck stiffness, rigors, confusion and purpuric rash over her hands and feet. CSF polymerase chain reaction (PCR) resulted for Neisseria meningitidis. Nasopharyngeal reversed transcription (RT)-PCR was positive for COVID-19. After recovery, patient was discharge with no neurological deficit. A repeat nasopharyngeal throat swab for COVID-19 was negative.[22]

Mardani et al also reported a meningoencephalitis case in Iran associated with COVID-19 recurrence infection. A 64-year-old woman confirmed COVID-19 infection by RT-PCR. After getting treatment, the COVID-19 negative result was observed by RT-PCR. After a few weeks, the patient relapsed and had suggestive meningoencephalitis, she also had a positive COVID-19 result again by using three different samples from nasopharynx, tracheal aspiration, and CSF. However, COVID-19 serum antibodies were negative by the recombinant immunoblot assay technique.[23]

Dizziness

A retrospective case series of 138 hospitalized COVID-19 patients in China reported dizziness by 9.4%.[24] Previous systematic review study reported that 6.8% of COVID-19 patients suffered dizziness.[9] Another systematic review study also reported 13.9% of COVID-19 patients had dizziness.[25] However, the studies did not differ between vertigo and dizziness as COVID-19 clinical feature. Therefore, it needs further studies to understand the etiology of dizziness, example general weakness, stroke, and neuropathy.

Seizure

There are several issues between seizure and COVID-19. Firstly, seizure may be a symptom of viral invasion to the brain. Secondly, COVID-19 results in fatal pneumonia and causes severe hypoxemia, which may lead to brain injury. Thirdly, COVID-19 patients with history of epilepsy may have higher frequency and severity of seizure.[26]

A cross-sectional study in Wuhan, China, 8.56% of COVID-19 patients with history of epilepsy had increased seizure during the outbreak. Focal seizure was the most common seizure observed in this study (80.11%).[27] An increase in seizure frequency in COVID-19 patient with history of epilepsy was reported 29.5% by a cross-

sectional study conducted in Saudi Arabia. There was not much more different in type of seizure in this study (37.8% generalized seizure versus 32.7% focal seizure).[28]

A retrospective research in Boston showed that 0.7% of 1043 COVID-19 patients presented seizure as one the COVID-19 symptoms. 71% of those patients had generalized tonic-clonic seizure, while 29% had focal seizure.[29]

Peripheral nervous system

Anosmia

Olfactory dysfunction, including anosmia and hyposmia, frequently manifests as COVID-19 symptom. The incidence of anosmia is found higher in COVID-19 than it in another coronavirus.[30]

Goblet cells and ciliated cells are suggested to play an important role in anosmia due to COVID-19 infection.[31] These two cell types contain high concentration of ACE2, which is COVID-19 receptor, and TMPRSS2, which promotes COVID-19 infection. The sense of smell depends on the sensory cell. COVID-19 can damage sensory cell on the olfactory mucosa, which consists of epithelium cells, blood vessels, and axon from olfactory neurons, and initiate inflammatory response. The sensory cell is joined with the olfactory bulb by the cribriform plate, which allows for the transmission of sense of smell at the base of the frontal lobe as well as transmission of the virus to the brain. This pathway shows the possible linkage between CNS and PNS.[32]

A case series study in Italy found that 30% of COVID-19 patients had anosmia, which 25% of those patients were in home isolation and 38% of those patients were hospitalized.[33] Another research in Germany (72 patients) reported that 74% COVID-19 patients reduced a sense of smell.[34] A cross-sectional study in Iran also reported 69.09% of COVID-19 infection had hyposmia.[35]

Ageusia/dysgeusia

The expression of ACE2 in human body play an ultimate role in COVID-19 infection. ACE2 is expressed on the mucosa of oral cavity, which is found higher concentration in tongue than buccal and gingival tissue. This indicates potential mechanism of COVID-19 effect on the taste bud.[36]

Another suggestive mechanism is the sense of taste is affected by olfactory dysfunction. This mechanism may lead to the correlation between decreased sense of smell and taste.[37] A study done by Macera et al showed that 33% COVID-19 patients complain ageusia or dysgeusia.[33] A Germany study found that 69% COVID-19 patients decreased a sense of taste.[34] A decreased taste sensation was also reported by 83.38% of the COVID-19 patient in a study in Iran.[35]

Oculomotor nerve palsy

The oculomotor nerve palsy associated with COVID-19 was reported firstly in Wuhan, China. A 62-year-old man admitted to the hospital with history of diplopia and complete ptosis on the left eyelid. No history of common manifestations associated with COVID-19, such as cough, shortness of breath, fever, headache and chest pain were found. Inflammation markers were significantly elevated in this patient. Head imaging ruled out new infarction, bleeding of brainstem or pituitary apoplexy, tumor, multiple sclerosis, and aneurysm. Unenhanced CT-scan showed wide, multiple, diffuse ground-glass opacities in both lungs. Nasopharyngeal throat swab was positive for COVID-19. Therefore, the patient was diagnosed with oculomotor nerve palsy associated with COVID-19 infection as there was not found any underlying causes of oculomotor nerve palsy. The mechanism of how COVID-19 infected oculomotor nerve needs further understanding. The hypothesis suggests that oculomotor nerve palsy could be trigger by myelin and axon damage due to virus infection.[38]

Guillain-Barre syndrome (GBS)

GBS is an acute polyradiculoneuropathy which commonly presents with progressive monophasic generalized and symmetric weakness involving both upper and lower extremities and associated with hyporeflexia or areflexia.[39] Since COVID-19 pandemic, there have been some studies of the possible relationship between COVID-19 and GBS. COVID-19 are regarded as the etiology of GBS through neuronal capacities and inflammatory mechanism. The cytokine storm increase the level of IL-6 which stimulates inflammatory cascade and harms tissues.[40]

There are several studies about developing GBS in COVID-19 infection. Caress et al demonstrated that the mean time of the onset of nervous system manifestations, including paresthesia, limb weakness and cranial nerve symptoms, from the onset of COVID-19 was 11±6.5 days (range, 3-28 days). Limb paresthesia and weakness were the most frequently symptoms on the presentation. Acute inflammatory demyelinating polyneuropathy (AIDP, 64.8%) was the most common type of GBS, whereas acute motor axonal neuropathy (AMAN, 2.7%) was the least common type of GBS seen in this study.[41]

Sanctis et al presented that the mean time of the onset between COVID-19 infection to the symptoms of GBS was 9 days (range 8-24 days). In line with Caress et al this study also found AIDP (55.56%) as the most prevalent type of GBS, while AMAN (5.56%) was the least prevalent type of GBS.[42]

Muscle

Myalgia or arthralgia is reported as the common symptom of muscle involvement in COVID-19 infection. A study (1099 patients with confirmed COVID-19 positive), which

was done by Guan et al, presented 14.9% of the patients had myalgia or arthralgia. It was found much more in critically ill patients (17.3%) than those in non-critically ill patient (14.5%).[13]

Higher level of muscle enzymes, such as lactate dehydrogenase (>250 U/l) and creatinine kinase (>200 U/l) were also observed in 31% and 13.7% hospitalized COVID-19 patients, respectively. Both of the muscle enzymes level was found higher in severe ill patients (58.1% for lactate dehydrogenase and 19% for creatinine kinase) than those in non-severe ill patients (37.2% for lactate dehydrogenase and 13.7% for creatinine kinase).[13]

Mao et al also demonstrated that patients with muscle injury had significantly higher level of creatinine kinase than those without muscle injury in COVID-19 patients. In addition, creatine kinase and lactate dehydrogenase levels were found higher in severe patients than non-severe patients of COVID-19 infection.[12]

The lower level of muscle enzymes was shown in mild illness in a study of 62 COVID-19 infection patients in Zhejiang Province, China. 92% of the patients had creatinine kinase <185 U/L and 73% of the patients had lactate dehydrogenase <245 U/L. Therefore, the level of the muscle enzymes correspondences with the severity of COVID-19 infection.[14]

CONCLUSION

Although COVID-19 infection mainly manifests as pneumonia, there are several scientific evidences of neurological involvement in COVID-19 infection. Medical physicians must be able to recognize the neurological manifestations as COVID-19 clinical features in order to reduce the mortality rate. Medical physician must also rule out COVID-19 infection in patient presenting neurological disorders.

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