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Review Article

Neurological manifestations of coronavirus disease: a literature review

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ABSTRACT

In December 2019, coronavirus pandemic re-emerged. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been identified as the causation in series of acute pneumonia cases discovered in Wuhan in Hubei Province, China. This disease is officially named COVID-19 by WHO. Symptoms manifestation of COVID-19 range from fever, malaise, myalgia, headache, to respiratory system symptoms of cough, stuffy/runny nose, and difficulty breathing. In severe cases, it may result in ARDS. A case study has reported that COVID-19 may also have cardiovascular manifestation, i.e. life threatening arrhythmia. Although COVID-19 is a respiratory infection and cardiovascular event is the main cause of fatality, medical professionals must understand its neurological complications in order to reduce mortality rate in infected patients. Further researches on specific risk factors or determinant protective factors from the neurological symptoms are needed to reduce risk of complication in COVID-19 infection cases.

Keywords: COVID-19, Coronavirus, Neurological manifestations

INTRODUCTION

Two pandemic outbreaks caused by coronaviruses took place in the last 2 decades, they are SARS in 2003 and MERS in 2012. In December 2019, novel coronavirus pandemic re-emerged. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been identified as the causation in series of acute pneumonia cases discovered in Wuhan in Hubei Province, China. This disease is officially named COVID-19 by WHO. Coronavirus Disease (COVID-19) pandemics started in Wuhan, China and has spread rapidly to numerous countries. Even though the transmission process of this virus has not been fully understood, the significant increase in number of infection cases is evident of human to human transmission.[1,2] In a month, this virus has spread widely in China during the Lunar New Year festive period, which is typically celebrated in large gatherings and thus increasing the transmission potential. By 1 March 2020, SARS-CoV-2 has caused 80,981 confirmed COVID-19 cases in China, and 44,067 cases in 117 countries. Roughly 80% of confirmed cases are linked to Wuhan. The absence of effective anti-viral medication or vaccine and the existence of asymptomatic infected cases have made it hard for healthcare workers to detect, treat and reduce mortality rate of this viral infection. Presently, COVID-19 has been declared as Public Health Emergency of International by WHO.[1-4] Although COVID-19 is a respiratory infection and cardiovascular event is the main cause of fatality, medical professionals must understand its neurological complications in order to reduce mortality rate in infected patients.

REVIEW OF LITERATURE

Coronavirus disease 19 (COVID-19)

Coronavirus is non-segmented positive-sense single-stranded RNA [(+)ssRNA] virus with estimated 30kb genome encapsulated within protein envelope. Most coronavirus causes illness in its specific host, some are able to infect human through cross species transmission and poses health threat to community. Two serious pandemic outbreaks caused by coronaviruses took place in the last 2 decades, they are SARS in 2003 and MERS in 2012. In December 2019, novel coronavirus pandemic re-emerged as SARS-CoV-2 or COVID-19 as designated by WHO. [5,6]

SARS-CoV-2 has been shown to cause illness through mechanism analogous to coronavirus SARS, with potential damages to vital organs such as lungs, heart, liver and kidney and infection which induces high risk to patients with its high prevalence of pneumonia. Reproduction rate of SARS-CoV-2 is faster than both SARS-CoV and MERS-CoV. Infection from SARS-CoV-2 can present no or mild symptoms, thus facilitate its potential to spread and extend the duration of this epidemic.[5,7] As the first COVID-19 case indicate direct contact history to Huanan Seafood Wholesale Market in Wuhan, animal to human transmission was suspected as its contagion mechanism. However, in subsequent cases, the same link was not present. Therefore, it was deduced that this virus can also be transmitted from human to human, and that COVID-19 mainly spreads from patient exhibiting symptoms.[8]

Symptoms manifestation of COVID-19 range from fever, malaise, joint pain, headache, to respiratory system symptoms of cough, stuffy/runny nose, and difficulty breathing. In severe cases, it may result in ARDS. A case study has reported that COVID-19 may also have cardiovascular manifestation, such as life threatening arrhythmia.[9]

Some pieces of evidence reported gastrointestinal involvement, acute cardiac injury, and acute kidney injury due to COVID-19. But some researchers also reported a neurological manifestation of COVID-19. The followings are neurological manifestations that have been reported by various researchers.

NEUROLOGICAL MANIFESTATIONS

Study by Wang et al on 214 patients with confirmed COVID-19, 40 cases (18.7%) suffer from acute neurological symptoms which requires treatment in ICU. Neurological symptoms arise from brain hemorrhage and cerebral infarction. The causal relation between COVID-19 and brain hemorrhage has not been clearly established. However, COVID-19 is known to induce cerebral infarction by increase in D-dimer as a result of infection process. Formation of D-dimer in turn causes thrombotic vascular event that potentially leads to cerebral infarction.[10]

Investigation is also done by Ling Mao et al in China, where neurological incidents are shown in severe COVID-19 cases. It can manifest as central nervous system symptoms (dizziness, headache, cerebrovascular disorders, ataxia and epilepsy) and peripheral nervous system symptoms (hyposmia, hypogeusia and myalgia). In patients which exhibit these neurological symptoms, it is found that the lymphocyte and thrombocyte counts are low while blood urea level is elevated. While the exact mechanism is not yet understood fully, it is hypothesized that the infection causes Uremic Encephalopathy.[11,12]

Hashikawa also performs a study in which it is hypothesized that the pathological process of COVID-19 is similar to pathological process of SARS-CoV and MERS-CoV since all are within the same family of viruses. An experiment on mice shows that when the virus is administered intranasally, the virus is able to infiltrate the nervous system through olfactory nerves and then spreads to various parts of the brain including the thalamus and the brain stem. The exact process of how it traverses the nervous system is not axiomatic, but it is believed to be not through hematogenic or lymphatic route as viral particle is not detected in non-neuronal cells in the infected areas of the brain. Therefore, it is strongly suspected that the virus traverses through trans-synaptic transfer process. [13]

The precise route through which SARS-CoV or MERS-CoV transmits through CNS has not been reported. According to studies on SARS-CoV transmission, hematogenic or lymphatic routes are highly unlikely, especially in the early onset of the infection, since virus particle is almost undetected in non-neuronal cells in the infected area of the brain. Considering the high similarity between SARS-CoV and COVID-19, it is extremely likely that COVID-19 has the same potential. [13] Based on the epidemiological survey on COVID-19, median time from first onset of symptoms to dyspnea is 5 days, to hospitalization is 7 days, dan to intensive care is 8 days. Therefore, this periode is sufficient for the virus to infiltrate and damage neurons in the brain. In fact, it has been reported that several patients who are infected by COVID-19 show neurological signs such as headache (sekitar 8%), lowered level of consciousness, to brain stem failure in cardiorespiratory functions.[13] There is a case report from Asia Filatov in United States of America where a 74-year old male patient returned to AED due to worsening of fever and cough symptoms. The patient had travel history to the Netherland 7 days prior to arrival in USA. He was put under isolation. X-ray scan was performed and bilateral pleural effusion was found. Chest CT showed widespread bibasilar consolidation and subpleural opacity. COVID-19 test result was confirmed positive. In a matter of hours, there is a decline in mental status. CT Scan did not show any abnormality. EEG presented bilateral slowing dan focal slowing over left temporal region with spike wave. Patient was diagnosed as COVID-19 with encephalopathy.[14]

Acute Necrotizing Encephalopathy (ANE) is also reported to have occurred in COVID-19 patient. Neo Poyiadji et al reports a case where 54-year old female with initial complain of cough, fever and decline in mental status in 3 days and has been declared positive COVID-19 through nasopharynx swab test. CT Scan without contrast report shows symmetric hypoattenuation over bilateral medial thalami with CT Angiogram test result normal. Brain MRI shows hemorrhagic rim enhancing lesions on bilateral thalamus, lobus temporalis medial, and subinsular region. Imaging result tends to acute necrotizing encephalopathy as ANE has specific characterists in imaging, i.e. multifocal lesion which includes the thalamus. Hypoattenuating lesion on CT Scan and on MRI T2-FLAIR show presence of signal hyperintensities with hemorrhage.[15]

Nages also reported a case in Iran, where a 30-year-old woman came to the emergency department with complaints of a tonic-clonic seizure. She previously had complaints of fever and dry cough for 3 days. The seizure happens five times every 8 hours, aware after the episode of seizure. Nasal and pharyngeal samples were positive for COVID-19. According to Huang et al, COVID-19 triggers an inflammatory cascade, which produces inflammatory cytokines, such as interleukin 2,6,7,10, and TNF-alpha. IL-6, TNF-alpha, and C3 complement can cause neuronal hyperexcitability via activation of glutamate receptors and play a role in developmental of acute seizures.[16,17]

CONCLUSION

Although COVID-19 is a respiratory infection and cardiovascular event is the main cause of fatality, medical professionals must understand its neurological complications in order to reduce mortality rate in infected patients. Further researches on specific risk factors or determinant protective factors from the neurological symptoms are needed to reduce risk of complication in COVID-19 infection cases.

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