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BRAINSTEM DYSFUNCTION IN SARS-COV-2 INFECTION CAN BE A POTENTIAL CAUSE OF RESPIRATORY DISTRESS

(Review article)

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ABSTRACT

Covid-19 pandemic has captivated scientists to investigate if this new disease can affect the central nervous system (CNS). The most challenging symptoms of Covid-19 are related to respiratory distress, and most patients admitted in intensive care units cannot breathe by their own. Therefore, a crucial question is if respiratory distress can be partially explained by the CNS affection. SARS-Cov-2 is a beta-coronavirus that shares high similarities with SARS-CoV. The infection of SARS-CoV has been reported in the brains from both patients and experimental animals, where the brainstem was heavily infected. Those coronaviruses have been able to invade the brainstem via a synapse-connected route to the medullary respiratory center, where the infected regions included the nucleus of the solitary tract and nucleus ambiguous. The vagal afferent nerves from receptors in the lung communicate with the medulla and pons respiratory control centers to coordinate inspiration and expiration. This suggests that neuroinvasion of SARS-CoV-2 might play a role in the acute respiratory failure of Covid-19. Therefore, acute respiratory distress in Covid-19 can be partially explained by brainstem dysfunction, suggesting the needs of more specific and aggressive treatments with the direct participation of neurologists and neurointensivists.

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INTRODUCTION

The world is facing a terrible pandemic of coronavirus infectious disease 2019 (Covid-19),[1-8] caused by SARS-Cov-2, which has captivated scientists to investigate the way that this new disease can affect the central nervous system (CNS).[9-16] A crucial question is if respiratory distress, commonly found in this pandemic, is at least partially explained by CNS affection.

Respiratory viruses are the leading cause of acute respiratory diseases. Coronaviruses (CoVs) commonly cause enteric and respiratory diseases in animals and humans.[10, 17, 18]. Human CoVs were responsible of two worldwide outbreaks: the severe acute respiratory syndrome CoV (SARS-CoV) and the Middle East respiratory syndrome CoV (MERS-CoV).[17, 19-21] SARS-Cov-2 is a beta-coronavirus that shares similarities with SARS-CoV. So far, it is proposed that it binds by glycoproteins expressed on its surface to the receptor of the angiotensin-converting enzyme 2 (ACE2), which is distributed in the respiratory tract epithelium, the lung parenchyma and other areas such as the gastrointestinal tract, endothelial cells, among others.[18, 19, 22-24]

Nonetheless, extra-pulmonary symptoms have been described in these viruses, highlighting their capacity to cause neurological complications: febrile seizures, loss of consciousness, convulsion, ataxia, status epilepticus, encephalitis, myelitis, neuritis with several reports in experimental models.[9-11, 13, 19, 25-34] We have recently reviewed that anosmia and hypogeusia as significant alerting initial or unique symptoms of COVID-19.[35]

Curiously, neurotropic and neuro-invasive capabilities have been described in several of their hosts, including humans among them, leading to symptoms such as multiple sclerosis (MS) and encephalomyelitis. A rising amount of evidence demonstrates that neurotropism is one shared feature of CoVs. The infection of SARS-CoV has been

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reported in the brains from both patients and experimental animals, where the brainstem was heavily infected. Furthermore, some coronaviruses have been demonstrated able to spread via a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways.[1, 9-11, 19, 36, 37]

Most CoVs share a similar viral structure and infection pathway, and therefore the infection mechanisms previously found for other CoVs may also be applicable for SARS-CoV-2. Several routes used by neurotropic virus to reach CNS have been described, including transneural and hematogenous pathways. CoV has been described to reach the brain via olfactory bulb, spreading from this point forward into the CNS and the periphery.[1, 14, 15, 21, 38-43]

It has been discussed that human coronavirus (HCoV) reaches the CNS through the olfactory bulb, causing inflammation and demyelination. This pathway is an excellent mechanism to access CNS for viruses that enter the body intranasally. Olfactory nerve has the particularity to be in communication with the nasal epithelium and also with the olfactory bulb, the entryway to the CNS.[12, 44-49]

Experimental models have demonstrated that ablation of the olfactory nerve limits its neurotropic capacities in mice. As soon as the infection is established, the virus can spread to the whole brain and CSF in less than 7 days. Consequently, it has been reported that this virus can induce demyelination in studies of glial cultures.[50, 51]

Therefore, based on previous pandemics,[21, 52, 53] medical care should not be limited to the organs whose symptoms are moderately easy to be assess, such as lung, kidney, and liver, because the brain could be lethally affected. The potential neuroinvasion of SARS-CoV-2 must prompt physician to be attentive on the commencement of neurological symptoms, to achieve and early diagnostics, and neuroprotection.[17, 19, 20]

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Neurological symptoms in other viral pandemics

In 2009 a new H1N1 pandemic was the causative agent of high mortality rates and exhibited increased reports of neurological complications. According to Asadi-Pooya et al., a retrospective study of a sample of 55 patients infected with H1N1 detected a 50% of visible neurological symptoms.[54]

Several neurological complications have been observed in CoV epidemics: encephalitis, myelitis, meningitis, seizures, and Guillain-Barre syndrome (Sivadon-Tardy et al., 2009). ,[14, 16, 36, 55-57] Seropositivity for coronaviruses has been reported in a variety of neurologic disorders, which include encephalitis,11 optic neuritis,12 multiple sclerosis,13 and Parkinson disease. [57] [58, 59] Virus has also been isolated from the CSF and brain of patients with multiple sclerosis.15 Viruses implicated include HCoV-229E, HCoV-293, and HCoV-OC43. [57]

Hung et al. reported the first case of SARS-CoV infection with neurological manifestations in a 59-year-old woman with, in the year. The patient was initially admitted with swinging fever, chills, productive coughing and diarrhea, which eventually lead to oxygen requirements, vomit, seizures and episodes of four-limb twitching. SARS-CoV infection was established in tracheal aspirates and cerebral spinal fluid (CSF) samples.[57, 60]

SARS-CoV was isolated from the brain of a patient who had shown neurological deficits on 28th day of infection. This is concordance with previous studies from other coronavirus epidemics, stating that SARS-CoV, invades the CNS. Moreover, autopsies with immunohistochemistry, in situ hybridization, and electron microscopic techniques of brain tissue have confirmed SARS-CoV infection of neurons, showing neuronal degeneration, surrounded by edema. Hence, taking in consideration that both virus are

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taxonomically near identical, SARS-CoV-2 should present a very similar trend to affect the SNC.[9, 21, 57, 61]

Evidence of the COVID-19 Virus Targeting the CNS

The prognostic and diagnostic significance of neurological sign and symptoms in COVID-19 patients can be gauged by fact that the protocol designed to investigate the First Few X cases (FFX) and their close contacts by the World Health Organization (WHO), includes a separate section for "other neurological signs" in addition to separate columns for respiratory symptoms.[33] Additionally, reports of COVID-19-affected individuals experiencing convulsions is alarming and need to be distinguished from febrile convulsions, that is expected to occur with high-grade fever in patients with COVID-19.[9-11, 19, 44]

The dissemination of COVID-19 in the systemic circulation or across the cribriform plate of the ethmoid bone during an early or later phase of the infection can lead to brain infection of SARS-CoV. When the of SARS-CoV-2 virus enters the general circulation reaches the cerebral circulation, where the slow movement of the blood within the microcirculation, could be one of the factors that may facilitate the interaction of the SARS-CoV-2 virus spike protein with ACE2 expressed in the capillary endothelium. Subsequent budding of the viral particles from the capillary endothelium and damage to the endothelial lining can favor viral access to the brain. [10, 17, 19, 36, 62]

The brain expresses angiotensin converting enzyme 2 (ACE2) receptors that have been detected over glial cells and neurons, which suggest that these cells are potential targets of COVID-19. As can be found in endothelial cells of the brain, this raises the hypothesis that strokes linked with SARS-CoV-2 might be directly associated to the viral infection, and encephalitis could be a probable complication.[57, 60] A recent study of 214 patients

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complaining Covid-19, reported neurological manifestations in COVID-19 in 78 (36.4%), such as acute cerebrovascular diseases, consciousness impairment and skeletal muscle symptoms, suggesting a neurotropic potential for SARS-CoV-2 .[57] [63] Other study from Wuhan city of Covid-19 reported neurologic symptoms, such as headache (about 8%), nausea and vomiting (1%).[64]

The National Health Commission of China of the Diagnosis and Treatment Guidelines for COVID-19 published human histopathological studies finding edema and partial neuronal degeneration in brain tissues[65]. Other study reported the presence of SARS-CoV-2 in the cerebrospinal fluid (CPF) of a Covid-19 patient.[60]

These studies, without a reasonable doubt, validate our rationale of CNS being targeted by SARS-CoV-2, as pointed out recently.[57]

Brainstem dysfunction in SARS-CoV-2 infection as a potential cause of respiratory distress

It has been argued that almost all the βCoVs are not always limited to the respiratory tract and that they may also invade the CNS, leading to neurological complications. Hence, according to the high likeness between SARS-CoV and SARS-CoV2, it has been suggested that a neuroinvasion of SARS-CoV-2 plays a role in the acute respiratory failure of patients complaining COVID-19.[20, 44, 51]

SARS-CoV-2 causes acute, highly lethal pneumonia with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV.[19, 37, 61, 66] Chest computerized tomography (CT) scans in most patients with fever, dry cough, and dyspnea have shown bilateral ground-glass opacities. However, a main difference from SARS-CoV is that and SARS-CoV-2-infected patients infrequently showed prominent upper respiratory tract

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signs and symptoms, suggesting that the target cells of SARS-CoV-2 may be located in the lower airway.[67, 68]

The most characteristic and challenging symptoms of Covid-19 are related to a respiratory distress.[69-72] Wang et al. reported that about 46% to 65% of the patients About 46% to 65% of the patients admitted in the intensive care unit (ICU) deteriorated in a brief period of time and died because of respiratory failure. According to these data, about 89% of the patients in ICUs could not breathe by their own in the intensive care, worsening in a short period of time and dying due to respiratory failure.[68, 73]

Using transgenic mice it was possible to demonstrate that when SARS-CoV or MERS-COV were given intranasally, these viruses could enter the brain, probably via the olfactory nerves, rapidly spreading to specific brain areas, such as the thalamus and the brainstem.[44, 57, 74]

Based on clinical observations several authors have considered that the West Nile virus (WNV) presumptively causes lesions in the CNS that harmfully affect pulmonary function. WNV infects and causes lesions in the brain stem of human patients, which contains respiratory control functions in the medulla and pons. Another possible cause of WNV-induced EMG suppression is cytokine signaling of the vagal afferent nerves to central autonomic pathways.[75-77]

It has been widely supported that that lesions in the medulla can cause respiratory dysfunction, like in congenital central hypoventilation syndrome,[78] or severe brain injury,[79] which results in damage to medullar respiratory control function.[35, 80-84]

It is extremely important to remark that the brainstem has been severely infected by SARS-CoV34, 35 or MERS-CoV. It has been reported that viral antigens have been detected in the brainstem, where the infected regions included the nucleus of the solitary tract and nucleus ambiguous. Afferent axons from the carotid and aortic bodies in the

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glossopharyngeal nerve contain chemoreceptor cells, and vagal afferent nerves from receptors in the lung communicate with the medulla and pons respiratory control centers to coordinate inspiration and expiration, while the efferent fibers from the nucleus ambiguous and the nucleus of the solitary tract provide innervation to airway smooth muscle, glands, and blood vessels. Such neuroanatomic interconnections indicate that the death of infected animals or patients, due to respiratory distress, may be caused by dysfunction of the respiratory center in the brainstem.[11, 19, 42, 77, 85, 86]

Based upon the first-hand evidence from Wuhan local hospitals, the common symptoms of COVID-19 were fever (83%-99%) and dry cough (59.4%-82%) at the onset of illness. However, the most characteristic and deadly symptom of Covid-19 patients is respiratory distress. Among the patients with dyspnea, more than half needed mechanical respiratory support. About 46% to 65% of the patients in the intensive care worsened in a short period of time and died due to respiratory failure.[87-90] Wang et al. reported that 11.1% received high-flow oxygen therapy, 41.7% received noninvasive ventilation, and 47.2% received invasive ventilation. These data suggest that most (about 89%) of the patients in need of intensive care could not breathe spontaneously.

Conclusion:

With the recent COVID-19 outbreak, there is an urgent need to understand the neurotropic potential of the COVID-19 virus in order to prioritize and individualize the treatment protocols based on the severity of the disease and predominant organ involvement.[57]

It also important to remark SARS-CoV-2 can invade the brainstem leading to respiratory center dysfunction. [11, 19, 42, 77, 85, 86] Hence, serial neurological examinations are

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recommended, with an exhaustive exploration of brainstem reflexes. As Neuroimaging techniques are not always easy to use in ventilated patients, ancillary tests, such as brainstem auditory and somatosensory evoked potentials, quantitative EEG, transcranial Doppler, can be used to monitor brain function in severe-acute Covid-19 patients.

Therefore, acute respiratory distress in Covid-19 can be partially explained by brainstem dysfunction, suggesting the needs of more specific and aggressive treatments with the direct participation of neurologists and neurointensivists.

Hence, in patients complaining Covid-19 admitted in ICUs due to acute respiratory failure, a brain complication should be considered for protocol treatments.

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