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LETTER TO THE EDITOR

Neuropathogenesis in COVID-19

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To the Editor:

SARS-CoV-2 or COVID-19 is a new human coronavirus that emerged in Wuhan, China in late 2019 and is currently causing a pandemic (1, 2). With the possibility of future outbreaks of the disease, it may manifest with diverse clinical characteristics and different severity, as has been seen with other viruses. COVID-19 belongs to a large family of RNA viruses that have been considered a global health problem because they have a remarkably high transmissibility potential and sometimes invade the CNS (3–5). Because of the rapid expansion of a virus that until now was unknown, it is important to understand the mechanisms by which COVID-19 generates CNS disease. Understanding CNS involvement in the disease is especially challenging and current theories of pathogenesis include direct neuroinvasion, crossing of the blood–brain barrier (BBB) by the virus, and a nicotinic hypothesis.

NEUROPATHOGENESIS IN COVID-19

The CNS is vulnerable to viruses and many, such as herpes viruses, arboviruses, measles, influenza, and HIV, enter the brain and cause neurological disease (6). Coronaviruses can also act on the CNS (4, 7), and this is why in a pandemic, high numbers of infections could result in the appearance of neurological conditions. Indeed, 36% of those affected by COVID-19 with neurological manifestations have been reported (8). Coronaviruses are neurotropic and can affect both neurons and glial cells thereby inducing various neurological pathologies (neurovirulence) (4). With respect to the similarity of COVID-19 with SARS-CoV-1 (causing the epidemic of 2006–2007), it is postulated that COVID-19 accumulates mainly in the nasal epithelium and the lower respiratory tract (4). The appearance of early symptoms in the form of loss of smell (anosmia), imbalance and/or impaired gait (ataxia), and seizures should be considered as neurological manifestations of COVID-19 infection (9). Specifically, coronaviruses have been reported to cross the BBB (10), and 3 common virus routes to cross the BBB have been previously reported (11): direct infection of endothelial cells that comprise the BBB; crossing permeable regions of the BBB; and infection of cells that cross that barrier, often referred as the Trojan horse approach (12). However, it is unlikely that COVID-19 can do so, due to the size of this virus, making it more likely to access via olfactory (13) or trigeminal nerves, which would explain the anosmia prevalence in this pandemic. The initial mechanism of infection appears to be the recognition by the spike of COVID-19 of the receptor for angiotensin-converting enzyme 2 (ACE2), which in humans is expressed in the capillary endothelium of the brain and other organs (14). Recently, the presence of COVID-19 has been reported in autopsy samples in the CNS endothelial cell surfaces and within areas adjacent to necrotic areas in infected patients (15). Furthermore, SARS-CoV-1 has been isolated from brain tissue in autopsies using immunohistochemistry, in situ hybridization, and electron microscopic confirmation of viral infection of neurons (16). However, mechanisms of CNS involvement of COVID-19 may not be mutually exclusive and both the theory of direct neuroinvasion (hypothesis of synaptic propagation and hypothesis of ACE2) and the nicotinic hypothesis may be valid.

DIRECT NEUROINVASION HYPOTHESIS

This hypothesis is based on the following lines of evidence (17): (1) extrapolated biological plausibility of CNS involvement by other respiratory viruses; (2) neurological damage by a coronavirus in other species; (3) animal models of CNS infection by human coronaviruses; (4) the existence of neurological complications from other coronaviruses; and (5) COVID-19 patients who have presented neurological manifestations.

Li et al reported that COVID-19 patients have respiratory distress and are sometimes unable to breathe spontaneously. Additionally, they may show neurological signs, such as headache, nausea, and vomiting (2). Growing evidence shows that coronaviruses are not always limited to the respiratory tract but can also invade CNS and cause neurological disease. In fact, SARS-CoV-1, the most closely related human coronavirus, has been seen in the brains of patients and experimental animals, where the brainstem was severely infected (6); and COVID-19 has been identified in CSF (18).

Previous studies have demonstrated the ability of coronaviruses to cause neuronal death in mice through invasion of the CNS by the cribriform plate of ethmoid and subsequent invasion of the olfactory neuroepithelium (19). Coronaviruses may spread through synapses from the neurons of the olfactory nerve to the cardiorespiratory center and from there reach the lungs through the medulla, ending in the afferent neurons located in the lung for their respiratory control (theory of synaptic propagation). This suggests how Covid-19 neurotropism may contribute to respiratory failure. When the virus enters the body through the nerves and/or the lung, it would lead to different clinical characteristics with different results. This pathway has been described in many viruses, and even prions, through the peripheral nervous system (12). COVID-19 could directly penetrate sensory nerve endings and travel through retrograde axonal flow as other coronavirus (20). It is worth noting the role of the trigeminal nerve at the entrance to the CNS since cases of conjunctivitis have been reported (21); the asymptomatic presence of COVID-19 on the ocular surface only has been reported as an exit route. Another route of neuroinvasion less probable is that described in prions (22). Prions accumulate in sympathetic nerve endings within lymphoid organs, which are a reservoir of infectivity. Through sympathetic nerves, prions spread to the CNS where they replicate in neurons, causing their destruction in encephalopathies. Direct neuroinvasion contrasts with the currently accepted view that ACE2 is the primary receptor for COVID-2 for its entry into cells.

The second line of argument that underlies the neuroinvasion hypothesis comes from Baig et al (13, 14). In the short time since the beginning of the outbreak, it has been shown that, (similar to SARS-CoV-1), COVID-19 exploits the ACE2 receptor to penetrate into cells. In the brain, ACE2 is expressed in neurons, glia, and endothelial cells and is particularly present in the brainstem and in the regions responsible for the regulation of cardiovascular functions, including the subfornical organ, paraventricular nucleus, nucleus of the solitary tract, and rostral ventrolateral medulla (23). Once inside the neuronal tissue environment, COVID-19 interaction with ACE2 receptors expressed by neurons can initiate a cycle of viral gemmation accompanied by neuronal damage without substantial inflammation, as previously seen with SARS CoV-1. This would explain the mildness of symptoms in a large number of cases of COVID-19. Several studies have reported that some patients infected with COVID-19 show neurological symptoms such as headache (about 8%), nausea, and vomiting (1%) (24). However, cases of SARS-Cov-2 encephalitis and its presence in CSF have also been recorded (14, 24, 25). Regarding endothelial cell involvement, the emphasis has recently been placed on a "cytokine storm" and neuroinflammation (26). Cytokine storm, also called macrophage activation syndrome, is a systemic inflammatory response that can be triggered by a variety of factors such as infections and drugs (27).

NICOTINIC HYPOTHESIS

The relationship between nicotine and ACE2 has been explored in the framework of cardiovascular and lung diseases (28). Angiotensin- (1–7) or ANG (1–7) is a heptapeptide of the renin angiotensin system (RAS) generated from angiotensin 2 (ANG 2) and angiotensin 1 (ANG 1) through ACE2, among other enzymatic routes. ANG (1–7) binds to the G protein-coupled metabotropic receptor MAS (29). It is considered a physiological antagonist of ANG 2, so it is postulated that ANG (1–7) and other MAS agonists could reduce various deleterious actions of ANG 2 in the brain and other body organs (29). In the ACE-angiotensin 2 (ANG 2)-angiotensin receptor type 1 (AT1R) system, nicotine increases the expression and activity of renin, ACE, and AT1R, while in the compensatory axis ACE2/ANG-(1–7)/MAS, nicotine downregulates the expression and/or activity of ACE2 and AT2R. This suggests a possible contribution of nicotinic acetylcholine receptors (nAChR) in the regulation of ACE2. Although a lower incidence of COVID-19 has been described in smokers (30), this possibility has not yet been explored in the framework of viral neuroinfections (31). Furthermore, these pathways might be therapeutic targets in COVID-19 infection.

On the other hand, various coronaviruses have been identified by serological techniques in a wide variety of neurological pathologies, such as Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and optic neuritis (5, 20, 32, 33). The viral persistence of Nidovirus (coronavirus) in central nervous system (CNS) was described by Lavi et al (34). Coronaviruses 229E, 293, and OC43 have been isolated from the cerebrospinal fluid (CSF) and the brain of patients with multiple sclerosis (33). The immune response after infection could participate in the induction or exacerbation of multiple sclerosis outbreaks in susceptible individuals (4). This would also support the idea that apparent reinfections of COVID-19 patients who recovered from the disease, return to suffer it with or without neurological symptoms due to the persistence of the virus in neural tissue. This scenario is described in varicella-zoster virus infection (35, 36). In a small group of COVID-19 cases, there was a suggestion of evidence for reactivation of the virus, which has no specific clinical characteristics to distinguish it from primary infection.

In the case of COVID-19, the study of the involvement of the nervous system in the pathogenesis of the disease is especially interesting and more innovative theories may explain not only neurological complications but the primary infection and the involvement of the various organs and systems.

Conflict of Interest

Marcos Altable and Juan Moisés de la Serna have no conflicts of interest to disclose regarding the manuscript.

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