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Viewpoint

Autonomic Brain Centers and Pathophysiology of COVID-19

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ABSTRACT: Accumulating data have now shown strong evidence that COVID-19 infection leads to the occurrence of neurological signs with different injury severity. Anosmia and agueusia are now well documented and included in the criteria list for diagnosis, and specialists have stressed that doctors screen COVID-19 patients for these two signs. The eventual brainstem dysregulation, due to the invasion of SARS CoV-2, as a cause of respiratory problems linked to COVID-19, has also been extensively discussed. All these findings lead to an implication of the central nervous system in the pathophysiology of COVID-19. Here we provide additional elements that could explain other described signs like appetite loss, vomiting, and nausea. For this, we investigated the role of brainstem structures located in the medulla oblongata involved in food intake and vomiting control. We also discussed the possible pathways the virus uses to reach the brainstem, i.e., neurotropic and hematogenous (with its two variants) routes.

KEYWORDS: *Coronavirus, COVID-19, central nervous system, food intake control, nausea and vomiting*

It is well-known now that the viral disease caused by a new coronavirus named "coronavirus disease 2019" (COVID-19) provoked a large-scale epidemic beginning in China and affecting all countries worldwide. The acute respiratory disease caused by the virus represents a serious public health issue. The World Health Organization raised the threat by this epidemic to the "very high" level, on February 28, 2020. The classical hallmark symptoms of the disease reported for most of the infected patients include fever, cough, and shortness of breath, distinguishing COVID-19 from a cold or flu hyperthermia. Those signs do appear in many if not most of the severe cases. Although the pathogenic agent is qualified as a virus with many unknowns, progressively accumulated data worldwide indicate other uncommon symptoms associated with SARS-CoV-2 like dermatological, gastrointestinal, and neurological issues. Many recently published papers reported on several clinical signs that could be classified as neurological alterations, supporting the ability of SARS-CoV-2 to attack human brain and also the eventuality of the involvement of the brain in the physiopathology of SARS-Cov-2. The link between COVID-19 and neurological problems has not been fully determined, and several cases with neurological disorders have been cited and discussed in previous studies. The neurological signs associated with SARS-CoV-2 could be categorized in two types. In the first group, studies documented hyponosmia/anosmia and hypogueusia/agueusia in COVID-19 patients mildly affected by the virus and, therefore, not requiring respiratory assistance. This led many doctors in different countries to look for these symptoms in people who otherwise are not extremely ill or are not ill. On the other side, neurological signs like mental confusion (loss of bearings, disturbance of alertness), disturbance of higher functions, restlessness, or loss of consciousness have been principally reported in severe cases.[1] Other neurological signs qualified as less common symptoms including headache, abdominal pain, diarrhea, nausea, and vomiting have also been reported. Patients with digestive symptoms had a longer time from symptom onset to hospital admission than patients without digestive symptoms. Nausea and vomiting symptoms could be of high interest as they suggest disturbances in the central regulation of food intake and also the impairment of the brain structure involved in the control of vomiting and nausea. Loss of appetite has also been shown to occur at earlier stages of infection.[2] Interestingly, both structures belong to the dorsal vagal complex (DVC) located in the medulla oblongata, the lowest region of the brainstem that controls several autonomic activities, including the heart, breathing, and food intake. Thus, injuries of this specific region of the brainstem could be detrimental for the maintenance of homeostasis. In the DVC, the nucleus of tractus solitarii (NTS) is known besides the hypothalamus (the classical brain center involved in food intake: FI control) to be a key area involved in the regulation of FI. We documented already on the eventual involvement of this nucleus and principally its subnucleus, i.e., the genatinous nucleus in the respiratory failure, in severe cases based on our previous observations in sudden infant death syndrome (SIDS) with neurochemical alteration of the catecholaminergic system.[3] Thus, the impairment of one discrete structure in the NTS could lead to significant functional alterations. Interestingly, the gelatinous nucleus is also known to be involved in food intake control.[4] The loss of appetite means that the crosstalk between the hypothalamus and DVC has been broken as in pathological states like stress as we reported

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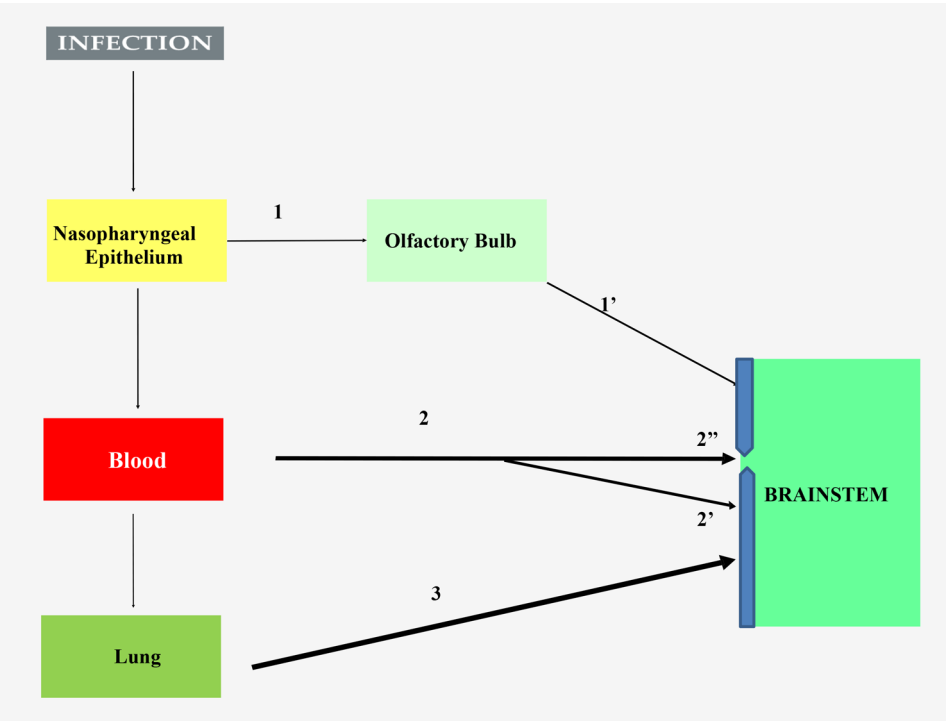

Figure 1. Schematic representation showing the possible entry routes of SARS-CoV-2 into the brainstem. The first proposed model suggests a passage from the nasopharyngeal cavity to the olfactory bulb (1), spreading then in the brain and reaching the brainstem (1′) by transsynaptic migration. The second one is called hematogenous (2), as the virus could reach the brainstem directly by general circulation with (2′) or without crossing the BBB (2″). Finally, the vagus nerve connecting the brain to the lungs facilitates the migration of the virus to the brainstem due to its neurotropism (3).

previously,[5] which could be induced by the presence of the virus (or viral particles) in one or both brain areas. This presence is expected to affect negatively the orexigenic/anorexigenic neuropeptide signaling and by consequence will lead to an anorexia-like state explaining this appetite loss.

Concerning nausea and vomiting symptoms, it is well established that another component of the DVC plays a crucial role in elicitation of this symptom, i.e., the area postrema (AP) lying beneath the fourth cerebral ventricle. This structure has been classified as the "emetic chemoreceptor trigger zone" as its destruction abolished the emetic response to cardiac glycosides (for review, see ref 6). The neurocircuits also encompass the two other structures of the DVC, NTS and dorsal motor nucleus of the vagus (DMNV). The presence of the virus in these DVC structures and principally in AP could elicit the two previously cited signs. Furthermore, the presence of ACE2 receptors, to which SARS-CoV-2 binds, in these brainstem regions is in favor of this action. But at this stage, the remaining question is how does SARS-CoV-2 reach this brain region? Some authors report on the possibility of the virus to enter the brain via the nasopharyngeal epithelium. By taking the path of the olfactory nerve, the virus reaches the olfactory bulb and spreads further to other parts. This hypothesis is supported by the neurotropism of the virus in analogy to SARS-CoV-1 and MERS viruses. Neurotropism could also occur at the level of the vagus nerve that terminates in the DVC in the brainstem where MERS and SARS virus deposits have been reported in intranasally inoculated mice. In this case too, it is not excluded that the high load of virus in the airways could also contribute to its passage via the vagus nerve as this connects the DVC to the lungs (Figure 1). Another possibility is that the virus could "navigate" to the brain via the general circulation and could pass through the blood-brain barrier (BBB), responsible for protecting the brain against infections. Indeed, the presence of pleomorphic spherical viral-like particles has been reported individually and in small vesicles of endothelial cells of the BBB in the postmortem brain of a COVID-19 patient. However, one cannot exclude the passage of the virus to reach directly via blood the DVC without crossing the BBB at the level of the AP (in the case of the DVC in brainstem) and median eminence (in the case of hypothalamus); both are circumventricular organs where the BBB is lacking (Figure 1). In summary, the potential role of autonomic brain control in the management of some physiopathological aspects observed in COVID-19 patients has been discussed notably in relation to appetite loss and nausea/vomiting signs. We also hope that our contribution can encourage neuroscientists to deeply explore the hypotheses given in this contribution for further elucidation of the link between the brain and neurological signs observed in SARS-CoV-1 infected patients.

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Author Contributions

F.C. and M.N. took the initiative to write the manuscript. F.C. wrote first draft of the manuscript. M.M. and M.N. contributed to writing the manuscript. All authors contributed to the critical review of the manuscript. All authors have read and approved the final version of this manuscript.

Notes

The authors declare no competing financial interest.

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