

# Comment on “The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients”

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## Abstract

We have read with great care and interest the article by Li et al. The authors provide interesting elements with respect to the possible entry of severe acute respiratory syndrome coronavirus 2 at the brain area and plead for an implication of the central nervous system in respiratory problems linked to coronavirus disease. Here we provide additional elements that support those observations, notably the role of brainstem structures located in the medulla oblongata in modulating respiration. We also discussed the possible pathways the virus uses to cross the brain blood barrier and reach the brainstem.

## KEYWORDS

central nervous system, coronavirus, COVID-19, respiratory tract

In this critically period that we live worldwide, it is of high interest to analyze all new scientific and medical aspects reported on coronavirus disease (COVID-19). In this sense, we read with great interest the review paper by Li et al.<sup>1</sup> that elegantly addressed what's called now, the “Neuroscience of COVID-19.” This observation is supported by numerous reports pointing out a non-negligible involvement of the brain in the pathophysiology of COVID-19. In this review paper recently published in the Journal of Medical Virology, the authors reported literature findings documenting brain injury in the context of COVID-19 and potential consequences on major disease symptoms including respiratory problems. Although some commentaries refuted any role of the brain in COVID-19 context, the authors cited above in their response provided convincing elements that support the neuroinvasion of central nervous system (CNS) by the virus.<sup>2</sup> Thus, based on recently published literature; neurologic manifestations and more likely neurologic symptoms, such as acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury have been reported in an important percentage of severe patients with COVID-19. Other neurological symptoms like loss of smell and taste in some cases have also been documented in their commentaries response. The authors reported that most of the patients in need of intensive care could not breath spontaneously. The fact that breathing regulation is associated with autonomic

functions and the respiratory control system is as part of the autonomic nervous system is in favor of an alteration of the controlling brain autonomic centers in these patients. Besides the description of a possible defect of brain centers located principally in brainstem known to be involved in the control of respiration, the authors reported on the presence of Middle East respiratory syndrome and SARS virus's deposits in the brainstem of intranasally inoculated mice. Accordingly, a part of respiratory failure could be effectively attributed to an injury of brainstem centers located in medulla oblongata. Indeed, the nucleus of the solitary tract (NTS), part of this area, is thought to be the primary structure that processes the respiratory load-related afferent activity and contributes to the modification of the breathing pattern via efferent projections to other structures in the brainstem respiratory neural network.<sup>3</sup>

When respiratory mechanical or metabolic challenges occurred, animals are able to adjust the breathing frequency and hence to maintain appropriate minute ventilation, that is, respiratory load compensation. The failure of such compensatory mechanism could be correlated to the breath difficulties experienced by patients with COVID-19.

Interestingly, such breath dysfunction has also been reported to be linked to the sudden infant death syndrome.<sup>4</sup> Indeed, this syndrome is known to display deficiencies in cardio-respiratory functions<sup>5</sup> correlated to an absence of immunoreactivity to phenyl N-methyl transferase

(enzyme converting noradrenaline in adrenaline), electively in nucleus gelatinosus, a subnucleus of NTS. The gelatinous nucleus is located in the caudal part of the NTS which is the principal site of termination for sensory afferents conveying respiratory related information from the lungs and peripheral chemoreceptors. This caudal part is also the site of one of three principal concentrations of brainstem respiratory neurons, the "dorsal respiratory group." The absence of adrenergic neurons in this case has been hypothesized to be involved in the failure of normal autonomic breathing control in these infants. To which extent this altered brain-lung crosstalk could be involved in COVID-19 with respiratory failure. To do so, these anatomical brainstem regions should be seriously studied in postmortem COVID-19 brain samples. This is supported by the recently published study by Paniz-Mondolfi et al,<sup>6</sup> that confirmed by using electron microscopy, the presence of viral particles showing typical morphological properties of betacoronavirus<sup>6</sup> Another aspect that should be investigated is the exact route by which the virus reaches the brain areas. Authors of the article and a recent review performed by Yashavantha Rao and Jayabaskaran<sup>7</sup> reported that CoVs may first invade peripheral nerve terminals, and then gain access to the CNS via a synapse-connected route, they state on contrary, that, hematogenous or lymphatic route seems impossible, especially in the early stage of infection. However, it is not excluded that when the virus load becomes important in general circulation, it could reach several brain parts, notably at the level of circumventricular organs (CVO), areas lacking a blood-brain-barrier (BBB). This is the situation in the dorsal vagal complex<sup>8</sup> containing area postrema, a CVO which is situated close to the NTS. It is not excluded that the virus reaches directly the NTS by crossing the BBB. The presence in postmortem brain of a patient with COVID-19 of Pleomorphic spherical viral-like particles observed individually and in small vesicles of endothelial cells strongly support this hypothesis.<sup>6</sup> Furthermore, this observation is of high interest and in favor of the occurrence of the hematogenous entry route.

The paper discussed here is a great starting point that should stimulate investigations about the potential role of autonomic brain control in the management of respiratory failure observed in patients with COVID-19. We also hope that our comments raised herein can stress neuroscientists to deeply explore these hypotheses for a more elucidation of the role of brain in this pandemic.

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#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### AUTHOR CONTRIBUTION

FC and MN took initiative to write the manuscript. FC wrote first draft of the manuscript. MM and MN 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.

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