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COMMENTARY

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Hypoxemia in COVID-19; Comment on: "The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients"

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We read with interest the communications by Li et al[1,2] and Chigr et al,[3] suggesting that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targets the brainstem and plays a role in coronavirus disease 2019 (COVID-19) respiratory failure. Here, we hypothesize that asymptomatic hypoxemia (silent hypoxemia) presented by COVID-19 patients with severe pneumonia is related to a dysfunction of cortical rather than of subcortical structures.

Patients with COVID-19 seldom complain of dyspnea.[4,5] Breathing control is a complex phenomenon. Sensory afferent information arising from chemoreceptors (sensing pH, PaO2, and PaCO2), upper airways stretch receptors (sensing inflation or deflation of the lungs), and chest wall mechanoreceptors (sensing muscles tension and contraction) reach the *nucleus tractus solitarius* (NTS) in the *medulla oblongata*. The NTS is the main autonomic brain center involved in breathing control (master regulator); it processes and projects the afferent signals to higher cortical centers, such as the insula, and the sensory and motor cortices (integrated system).

Dyspnea is the subjective experience of breathing discomfort. It results from complex mechanisms, especially from a mismatch between efferent motor commands from the central nervous system (CNS) to the respiratory system, and afferent sensory informations (eg, expected airflow, cage movements) from the respiratory system to the CNS.[6] The insular cortex is essential for conscious experience of visceral perceptions elicited by interoceptive stimuli.[7] Perception of labored breathing involves the activation of the insula, insular lesions are associated with blunted perception of dyspnea.[8]

SARS-CoV-2 is a *β-coronavirus*, like HCoV-OC43 and SARS-CoV, to which is structurally homologous. These viruses are potentially neuroinvasive[2]; hence, the neuroinvasive potential of SARS-CoV-2 is probable. The olfactory disturbances common of COVID-19 can be due to virus-induced neuronal damage in the olfactory bulb.[9] Retrograde axonal transport can then enable propagation of SARS-CoV-2 toward the insula. Animal studies support this hypothesis: HCoV-OC43 and SARS-CoV can reach the CNS via the olfactory bulb and cause neuronal death[10,11]; moreover, the spreading of SARS-CoV to cortical structures occurs more rapidly compared to brainstem.

The virus could also entry the CNS via an hematogenous route, of which endotheliitis can be the backbone.[12] To note, brain tissue highly express SARS-CoV-2 cell receptor, the angiotensin-converting enzyme 2.[13]

To conclude, we hypothesize that *la belle indifference* (ie, the beautiful indifference) about breathlessness of COVID-19 depends on propagation of SARS-CoV-2 from the nose to the cortical regions, and subsequent virus-induced dysfunction. Isolated brainstem involvement as the sole and unique center involved in COVID-19 respiratory failure seems unconvincing. Brainstem mechanisms (necessary and sufficient to produce ventilator command and adapt it to the needs of the body) seem unaffected, as suggested by a normal to low pCO2 levels even in critically ill patients.[6,14] Nevertheless,

since brainstem conveys information to higher CNS structures involved in breathing control, its dysfunction can affect this integrated system and contribute to the respiratory symptoms (or their absence) of COVID-19 patients. Interestingly, peripheral afferents could also play a role: virus-induced C fibers dysfunction could contribute to the absence of dyspnea in COVID-19 pneumonia.[5]

La belle indifference is more than a wink to Charcot and Freud: recent studies support a role of the insula (among other cortical areas) in the unawareness described in functional disorders.[15]

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REFERENCES

1. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol*. 2020.
2. Li YC, Bai WZ, Hashikawa T. Response to Commentary on "The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients". *J Med Virol*. 2020.
3. Chigr F, Merzouki M, Najimi M. Comment on "The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients". *J Med Virol*. 2020.
4. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.
5. Bertran Recasens B, Martinez-Llorens JM, Rodriguez-Sevilla JJ, Rubio MA. Lack of dyspnea in Covid-19 patients; another neurological conundrum? *Eur J Neurol*. 2020.
6. Adler D, Janssens JP. The pathophysiology of respiratory failure: control of breathing, respiratory load, and muscle capacity. *Respiration*. 2019;97:93-104.
7. Namkung H, Kim SH, Sawa A. The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. *Trends Neurosci*. 2017;40:200-207.
8. Schön D, Rosenkranz M, Regelsberger J, Dahme B, Büchel C, von Leupoldt A. Reduced perception of dyspnea and pain after right insular cortex lesions. *Am J Respir Crit Care Med*. 2008;178:1173-1179.
9. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. 2020.
10. Conde G, Quintana Pájaro LD, Quintero Marzola ID, Ramos Villegas Y, Moscote Salazar LR. Neurotropism of SARS-CoV 2: mechanisms and manifestations. *J Neurol Sci*. 2020;412:116824.
11. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol*. 2008;82:7264-7275.
12. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417-1418.
13. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty*. 2020;9:45.
14. Zhang B, Zhou X, Qiu Y, et al. Clinical characteristics of 82 death cases with COVID-19. *medRxiv*. 2020. https://doi.org/10.1101/2020.02.26.20028191
15. Boeckle M, Liegl G, Jank R, Pieh C. Neural correlates of conversion disorder: overview and meta-analysis of neuroimaging studies on motor conversion disorder. *BMC Psychiatry*. 2016;16:195.

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