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LETTER TO THE EDITOR

Beyond silent hypoxemia: Does COVID-19 can blunt pain perception? Comment on "The neuroinvasive potential of SARS CoV2 may play a role in the respiratory failure of COVID 19 patients"

Dear Editor,

In our response to Li et al.[1] and Chigr et al.,[2] we suggested that asymptomatic hypoxemia in coronavirus disease 2019 (COVID-19) could be due to the propagation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) toward cortical regions, particularly the insula.[3]

A 70-years-old patient was admitted for COVID-19-ARDS necessitating high flow nasal cannula oxygenation (HFNCO) and continuous positive airway pressure. His evolution was favorable, and he was weaned from HFNCO on day 4. Symptoms onset started 12 days before hospitalization; 6 days after, reverse transcription polymerase chain reaction nasopharyngeal swab was positive. Although he never complained of dyspnea, the patient progressively had to stop for breathing when walking. Following admission to the hospital, oxygen saturation was 75%. Interestingly, the patient stated that his chronic back pain had completely disappeared since the onset of his respiratory symptoms. Apart from diffuse, fine crackles upon lung auscultation, his physical examination was normal. The neurological exam showed only diminished perception of nociceptive stimuli throughout the whole body, without modification of temperature sensibility; cognitive functions were normal. Brain imaging was deemed unnecessary. At the 1-month follow-up, the patient had fully recovered from his COVID-19 respiratory illness. However, he felt that his back pain was slowly reappearing.

Besides asymptomatic hypoxemia, the patient presented another interesting phenomenon: blunted pain perception. Lay journals have described anecdotal cases of a reduced pain threshold in COVID-19 patients.[4] Apart from reduced oral chemesthesis,[5] pain perception modulation in COVID-19 patients has never been described.

The SARS-CoV-2 spike protein can modulate nociception in a mouse model,[6] and human dorsal root ganglia sensory neurons express the ACE-2 receptor (SARS-CoV-2 "entry receptor").[7] Although many reports demonstrate an immune-mediated effect of SARS-CoV-2 on the peripheral neurological system, the involvement of small-fiber sensory neurons in COVID-19 is controversial.[8]

Here, we describe, for the first time, a patient in which SARS-CoV-2 infection resulted both in asymptomatic hypoxemia and in temporary blunted pain perception. Propagation of SARS-CoV-2 from the nose to the cortex (in particular the insula) and virus-induced dysfunction can affect dyspnea perception.[3] The insula is essential for interoception (i.e., the conscious experience of body signals). Besides breathing, the insula is implicated in pain modulation,[9] and its dysfunction plays a crucial role in chronic pain.[10] Interestingly, the insula is also known to respond to chemesthetic stimulations.[11]

We hypothesize that virus-mediated dysfunction of a focal cortical region, the insula, can result both in lack of dyspnea and in blunted pain perception. Future studies should evaluate the prevalence of the co-occurrence of silent hypoxemia and pain modulation and disentangle if SARS-CoV-2 has a specific tropism for the insula. Thus, COVID-19-induced *belle indifference* can extend beyond breathing. According to Newton: "Nature does nothing in vain when less will serve; for Nature is pleased with simplicity…".[12]

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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;92:552-555.
2. 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;92:703-704.
3. Coen M, Allali G, Adler D, Serratrice J. Hypoxemia in COVID 19; Comment on: "The neuroinvasive potential of SARS CoV2 may play a role in the respiratory failure of COVID 19 patients". *J Med Virol*. 2020;92:1705-1706.
4. Sutherland S. What we know so far about how COVID affects the nervous system. *Scientific American*. October 22, 2020. https://www.scientificamerican.com/article/what-we-know-so-far-about-how-covid-affects-the-nervous-system/#:~:text=Many%20of%20the%20symptoms%20experienced,weeks%20to%20months%20after%20infection
5. Parma V, Ohla K, Veldhuizen MG, et al. More than smell-COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chem Senses*. 2020;9(45):609-622.
6. Moutal A, Martin LF, Boinon L, et al. SARS-CoV-2 spike protein co-opts VEGF- A/neuropilin-1 receptor signaling to induce analgesia. *Pain*. 2020.
7. Shiers S, Ray PR, Wangzhou A, et al. ACE2 and SCARF expression in human DRG nociceptors: implications for SARS-CoV-2 virus neurological effects. *Pain*. 2020;161:2494-2501.
8. Oaklander AL. Clinical significance of angiotensin-converting enzyme 2 receptors for severe acute respiratory syndrome coronavirus 2 (COVID-19) on peripheral small-fiber sensory neurons is unknown today. *Pain*. 2020;161:2431-2433.
9. 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.
10. Harte SE, Ichesco E, Hampson JP, et al. Pharmacologic attenuation of cross-modal sensory augmentation within the chronic pain insula. *Pain*. 2016;157:1933-1945.
11. Rudenga K, Green B, Nachtigal D, Small DM. Evidence for an integrated oral sensory module in the human anterior ventral insula. *Chem Senses*. 2010;35:693-703.
12. Newton I. *The principia, mathematical principles of natural philosophy* (a new translation). Bernard Cohen I, Whitman A, trans-ed. Assisted by Budenz J. Berkeley: University of California Press; 1999.