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COMMENTARY

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Dyspnea: The vanished warning symptom of COVID-19 pneumonia

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Since December 2019, SARS-CoV-2 has rapidly spread worldwide, challenging the clinician and focusing the entire globe on critical illness high mortality.[1] Apart from common respiratory symptoms, patients often present with symptoms suggestive of SARS-CoV-2 neuroinvasiveness.[2] Some are very general (like headache, nausea, or vomiting), while others are more specific, such as hypoacousis, agueusia, or anosmia. SARS-CoV-2 is suspected to enter the central nervous system through the olfactive bulb and to progress transsynaptically to the brain—a mechanism demonstrated in animal models of SARS-CoV-1 infection.[2]

Dyspnea, a subjective experience of breathing discomfort, has been reported to affect less than 50% of SARS-CoV-2 infected patients and is more common in patients who will die compared to those who will recover.[1] The prevalence of dyspnea is barely higher in patients who develop acute respiratory distress and have the poorest clinical outcomes. Furthermore, the time from symptom onset to hospital admission is longer in patients who ultimately die than in those who survive.[1] This could either result from poor awareness of symptom gravity in the community or from patients' own poor perception of labored breathing. Both hypotheses may explain why two-thirds of patients hospitalized in the intensive care unit (ICU) in the Seattle region were directly admitted from home.[3] The value of dyspnea, as a warning symptom in COVID-19 pneumonia, therefore seems low. Yet, dyspnea has been strongly associated with a poor prognosis in the general population, in patients with chronic obstructive pulmonary disease, and also in patients surviving acute hypercapnic respiratory failure.

Dyspnea requires the cognitive and affective processing of interoceptive information arising from the respiratory system. This involves a cortical dimension that is well illustrated by interferences between dyspnea and cognition. In a randomized controlled study involving 40 healthy high-functioning young adults, we showed that experimental dyspnea altered cognitive and motor tasks associated with cortical functions.[4] In line with the neuroinvasiveness of SARS-CoV-2, we posit that poor perception of labored breathing may proceed from a SARS-CoV-2-related defective cortical processing of respiratory signals. Dyspnea perception typically involves the activation of sensorimotor, cerebellar, and limbic areas, including the insula. Moreover, neurological lesions of the insula may blunt the perception of dyspnea.[5] Most of the time, brainstem response remains appropriate, as attested by the low arterial partial pressure of carbon dioxide at clinical presentation.[6] As several clinicians worldwide have observed, we have also observed "happy hypoxemia" (ie, hypoxemia without dyspnea) [7] in countless patients admitted for severe COVID-19 pneumonia.

To illustrate this point, we would like to share our experience at the intermediate care units (ICMU) of Geneva University Hospitals. The same admission criteria are used in the ICMU and the ICU, that is a fraction of inspired oxygen (FiO_2) more than 50% with oxygen saturation (SpO_2) less than 90%, following the revised recommendations for the triage for intensive care treatment under resource scarcity in Switzerland.[8] The only difference for admission to the ICU is the presence of clinical signs of respiratory distress (ie, use of neck muscles during inspiration, abdominal paradox during inspiration, expression of fear) used as a

surrogate marker of dyspnea.[9] Therefore, patients are carefully selected in the absence of respiratory distress to be treated non-invasively in the ICMU by continuous positive airway pressure and high-flow nasal oxygen only. Regarding the pharmacological treatments, every patient infected by SARS-CoV-2 was treated by an association of hydroxychloroquine and lopinavir/ritonavir (if no contraindication), according to the guidelines of the Geneva University Hospitals—this combination of treatments was similar between patients admitted to the ICMU and those in the non-high dependency medical ward.

Among the first 83 patients with COVID-19 pneumonia admitted to the ICMU, 60 (age 62.5 ± 11.7 years; 32% female) were admitted for worsening hypoxemic respiratory failure. FiO2 at admission was 59 ± 17%, respiratory rate 32 ± 5 per minute, and the PaO_2/FiO_2 ratio 17.1 ± 5.7 kPa. Among these 60 patients, 40 (67%) successfully returned to their initial nonhigh dependency medical ward, while only 20 (33%) were admitted to the ICU to receive invasive mechanical ventilation. As dyspnea seems to be underreported in patients with COVID-19 pneumonia, our observation highlights the importance of monitoring clinical signs of respiratory distress in patients unable to self-report dyspnea. Future neuropathological studies will further inform us of the damage of brainstem and cortical regions in deceased COVID-19 patients with dyspnea.

The neuroinvasiveness-related "vanishing" dyspnea hypothesis illustrates this dichotomy of having severe hypoxemia without dyspnea and may explain the high mortality in COVID-19 patients admitted (too late) in the ICU.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

GA, CM, OG, and DA contributed to the design and implementation of the study. GA, CM, OG, CMP, TS, and DA contributed to the data analysis and interpretation. All authors discussed the results and commented on the manuscript. All the authors reviewed and approved the final manuscript to be published.

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