Received: 1 June 2020 | Accepted: 9 June 2020

DOI: 10.1002/jmv.26158

COMMENTARY

JOURNAL OF MEDICAL VIROLOGY WILEY

The possible impairment of respiratory-related neural loops may be associated with the silent pneumonia induced by SARS-CoV-2

Bai-Hong Tan[1] | Yan Zhang[2] | Yue Gui[3] | Shuang Wu[3] | Yan-Chao Li[3]

[1]Laboratory Teaching Center of Basic Medicine, Norman Bethune Health Science Center of Jilin University, Changchun, Jilin, China

[2]Core facilities for School of Life Science, Jilin University, Changchun, Jilin, China

[3]Department of Histology and Embryology, College of Basic Medical Sciences, Norman Bethune College of Medicine, Jilin University, Changchun, Jilin, China

Correspondence
Yan-Chao Li, Department of Histology and Embryology, College of Basic Medical Sciences, Norman Bethune College of Medicine, Jilin University, 130021 Changchun, Jilin, China.
Email: liyanchao@jlu.edu.cn

Abstract

As compared to many other viral pulmonary infections, there existed several peculiar manifestations in the COVID-19 patients, including the "silence" of pneumonia in both mild and severe cases and a long intensive care unit stay for those requiring invasive mechanical ventilation. Similar silent pneumonia has been documented in the infectioninduced by H5N1 influenza virus HK483 and was found to result from the direct attack of the virus on the bronchopulmonary C-fibers at the early stage and the final infection in the brainstem at the late stage. The long stay of critical patients in the intensive care unit is possibly due to the depression of central respiratory drive, which resulted in the failure to wean from the mechanic ventilation. Carotid and aortic bodies and bronchopulmonary C-fibers are two key peripheral components responsible for the chemosensitive responses in the respiratory system, while triggering respiratory reflexes depends predominantly on the putative chemosensitive neurons located in the pontomedullary nuclei. In view of the findings for the H5N1 influenza virus, the silence of pneumonia induced by SARS-CoV-2 may be due to the possible impairment of peripheral chemosensitive reflexes as well as the damage to the respiratory-related central neurons.

KEYWORDS

acute respiratory distress, coronavirus, COVID-19, nervous system

1 | INTRODUCTION

Following the worldwide spread of two previously unrecognized coronaviruses (CoV), the severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), another CoV, SARS-CoV-2, emerged as a highly contagious pathogen that spreads rapidly among human beings and has caused a worldwide outbreak of severe pneumonia (COVID-19) from the beginning of 2020.

As compared to many other viral pulmonary infections, there existed several peculiar manifestations in the COVID-19 patients, including the "silence" of pneumonia in both mild and severe cases and a long intensive care unit (ICU) stay for those requiring invasive mechanical ventilation. The peculiar features are now attracting more and more attention, but the underlying mechanisms are not fully clear.

2 | THE PECULIAR MANIFESTATIONS IN PATIENTS WITH COVID-19

Pathological examination showed that the lungs from infected patients manifested significant pathological lesions, including alveolar exudative and interstitial inflammation, alveolar epithelium proliferation, and hyaline membrane formation. Consistently, imaging examination reveals that most COVID-19 patients showed characteristic ground-glass opacities on chest CT scans.

The available clinical data show that COVID-19 patients, whether mild or severe, all showed the bilateral distribution of patchy shadows or ground-glass opacity.[1,2] It is more surprising that similar CT abnormalities have also been observed in the asymptomatic patients with COVID-19, and there were no significant differences in individual signs, patterns, zonal predominance or extent of CT abnormalities between the asymptomatic and symptomatic patients.[3]

Although chest CT has revealed striking abnormalities in the lungs of COVID-19 patients, most of them showed only mild flu-like symptoms.[1,2] About 37.8% to 81.4% patients with COVID-19 showed cough, but expectoration was reported in only 22.0% to 48.8% severe and 10.3% to 35.9% mild patients.

As a useful warning symptom, dyspnea occurred much more frequently in many other viral pulmonary infections, for example, in 69% of patients infected with MERS-CoV, 95% with the respiratory syncytial virus, and 82% with influenza virus.[4] In the case of COVID-19, although hypoxemia occurred in both severe and mild patients, 28.4% to 72.0% severe and 81.0% to 96.8% mild patients did not present dyspnea.

Several researchers also noticed that despite severe hypoxemia, the mechanical characteristics of the lungs were relatively well preserved in the severe COVID-19 patients, which is rarely seen in other forms of acute respiratory distress syndrome. A possible explanation, provided by the authors, is the loss of lung perfusion regulation and hypoxic vasoconstriction.[5]

It has been noticed that the COVID-19 patients, who required invasive mechanical ventilation, were characteristic of a long ICU stay.[2,6] These patients could not be weaned from the invasive mechanical ventilation, even though they had recovered from pneumonia.[6] Depression of central respiratory drive, resulting from the impairment of brainstem respiratory center, has been suggested as one main reason for this peculiar manifestation.[6]

3 | THE POSSIBLE IMPAIRMENT OF RESPIRATORY-RELATED NEURAL LOOPS AFTER SARS-CoV-2 INFECTION

Dyspnea is known as a multi-dimensional cognitive output of respiratory sensation that is initiated by peripheral afferent fibers and processed through the brainstem to subcortical and supratentorial structures. Carotid and aortic bodies and bronchopulmonary C-fibers are two key peripheral components responsible for the chemosensitive responses in the respiratory system, which are crucial in maintaining life in mammals. On the central side, triggering respiratory reflexes depends predominantly on the putative chemosensitive neurons located in the pontomedullary nuclei.

Depression or deficit of ventilatory responses has previously been reported in the infection induced by a highly pathogenic H5N1 influenza virus, HK483. Animal experiments revealed that the HK483 virus attacked directly bronchopulmonary C-fibers and infected the vagal C-neurons in vagal nodose ganglion at the early stage of infection. Moreover, the virus was eventually found to invade into the brainstem and infect the chemosensitive neurons in the retrotrapezoid nucleus, raphe and locus coeruleus.[7]

In view of the findings on the H5N1 virus, it is possible that the poor sputum production and the subjective feeling lacking dyspnea in COVID-19 patients may be attributed to the possible impairment of the respiratory-related neural loops. The infection in bronchopulmonary C-fibers may be related to the hypercapnic ventilatory response induced by HK483 virus, while the infection of chemosensitive neurons in the pontomedullary nuclei will abolish hypoxic ventilatory response. However, normal or low arterial partial pressure of carbon dioxide has been detected in most cases with COVID-19, suggesting that the hypercapnic ventilatory response remains appropriate after SARS-CoV-2 infection.

Different from that reported for the H5N1 virus, SARS-CoV-2 nucleic acid has also been detected in the serum, especially in critically ill patients, which dramatically increased the risk of infection of glomus cells in the carotid and aortic bodies, a major sensor monitoring O_2 in the blood, whose afferent axons communicate with the medullary respiratory centers in response to the change of blood oxygen.

Besides the peripheral components, the poor perception of hypoxemia in the COVID-19 patients may also be attributed to a possible defective cortical processing of respiratory signals. SARS-CoV-2 genome or particles have been demonstrated in the cerebrospinal fluid or brain tissues from some COVID-19 patients, which clearly demonstrated that SARS-CoV-2 has the ability to enter the central nervous system. In a COVID-19 patient with severe anosmia and dysgeusia, abnormal MRI signals have been found in the right gyrus rectus and olfactory bulbs on the third day after the onset of the disease.[8] Ultrastructural study on samples from a postmortem patient with COVID-19 further revealed severe tissue damage involving neurons, axons and myelin sheath in the olfactory pathway and the brainstem.[9]

As mentioned above, the direct infection of respiratory-related neural loops has been demonstrated to be responsible for the silence of pneumonia induced by the H1N1 influenza virus. It is quite likely that this is also the case for the SARS-CoV-2 infection. Therefore, we propose that the peculiar manifestations in COVID-19 patients may be attributed to the possible impairment of peripheral chemosensitive reflexes as well as the damage to the respiratory-related central neurons. This conclusion will supplement our previous hypothesis,[10] and provide an important clue to revealing the mechanisms underlying the acute respiratory distress syndrome induced by SARS-CoV-2.

ORCID

Yan-Chao Li http://orcid.org/0000-0002-2884-9829

REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

3. Zhang R, Ouyang H, Fu L, et al. CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive patients from Wuhan city. *Eur Radiol*. 2020:1-10. https://doi.org/10.1007/s00330-020-06854-1
4. 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. https://doi.org/10.1111/ene.14265
5. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;201(10):1299-1300. https://doi.org/10.1164/rccm.202003-0817LE
6. Manganelli F, Vargas M, Iovino A, Iacovazzo C, Santoro L, Servillo G. Brainstem involvement and respiratory failure in COVID-19. *Neurol Sci*. 2020;10. https://doi.org/10.1007/s10072-020-04487-2
7. Zhuang J, Zang N, Ye C, Xu F. Lethal avian influenza A (H5N1) virus replicates in pontomedullary chemosensitive neurons and depresses hypercapnic ventilator response in mice. *Am J Physiol Lung Cell Mol Physiol*. 2019;316(3):L525-L536. https://doi.org/10.1152/ajplung.00324.2018
8. Politi LS, Salsano E, Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurol*. 2020. https://doi.org/10.1001/jamaneurol.2020.2125
9. Bulfamante G, Chiumello D, Canevini MP, et al. First ultrastructural autoptic findings of SARS-Cov-2 in olfactory pathways and brainstem [published online ahead of print May 13, 2020]. *Minerva Anestesiol*. 2020. https://doi.org/10.23736/S0375-9393.20.14772-2
10. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92:552-555. https://doi.org/10.1002/jmv.25728

How to cite this article: Tan B-H, Zhang Y, Gui Y, Wu S, Li Y-C. The possible impairment of respiratory-related neural loops may be associated with the silent pneumonia induced by SARS-CoV-2. *J Med Virol*. 2020;92:2269–2271. https://doi.org/10.1002/jmv.26158