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COVID-19

Reply to Letter response to "The Janus faces of SARS-COV-2 infection in myasthenia gravis and myasthenic crisis"

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To the Editor

We were pleased to receive the correspondence from colleagues in relation to our comment published in *Neurological Sciences* [1]. We are grateful for the opportunity to clarify some of the important and relevant issues raised by them.

As for the first point, since the original assessment by Jaretzki et al. [2], data might have been biased because of different definitions of myasthenic crisis (MC) including or excluding Myasthenia Gravis Foundation of America (MGFA) Classes, for instances patients in class IV. A long-standing goal is to reach a clear definition of MC in order to design higher-yield clinical trials and to tailor the treatments, including supportive feeding, invasive or non-invasive ventilation. In consequence, patients defined as having MC should be precisely scored as integral part of myasthenia gravis (MG) outcome [3].

Second, Rodrigues et al. [4] patients had worsening of weakness preceding or at the time of respiratory failure, which leads to classify them as having MC. This statement should be taken cautiously, because the distinction between a worsened myasthenic patient due to underlying MG as a result of COVID-19 and a not worsened MG patient with severe COVID-19 pneumonia is not so obvious, also for an experienced neurologist. MC weakness may develop within minutes to days and often intubated patients are sedated, limiting the ability to detect worsening myasthenic weakness contributing to respiratory failure [5].

Third, it is crucial the assessment of the causes of respiratory failure in MC during SARS-COV-2 infection. The COVID-19 pandemic has inspired new interest in understanding the fundamental pathology of acute respiratory distress syndrome (ARDS), which has been associated with severe coronavirus disease 2019. ARDS has long been recognized to be remarkably heterogeneous, with a wide range of causes, a broad spectrum of severity, and different degrees of impairment in oxygenation and distribution of the lung disease [6]. Despite ARDS related to COVID-19 (CARDS) is broadly similar to the classical virally mediated ARDS, several phenotypes have been described, such as CARDS with mild reductions in compliance associated with severe hypoxemia, which differ from the typical ARDS features. Nevertheless, the physiological change behind the different forms of CARDS and classic-ARDS is mainly due to the intrapulmonary shunt, which results in severe impairment of gas exchange [7].

Rodrigues et al. wrote that they used hypercapnia without hypoxemia or presenting before hypoxemia as a surrogate marker for muscle weakness. We agree with the authors in defining this approach as appropriate for the identification of patients with alveolar hypoventilation, due to neuromuscular weakness. Indeed, despite also patients suffering from ARDS or CARDS exhibit impaired CO_2 clearance, mainly due to "wasted" ventilation in lung regions, where ventilation markedly exceed perfusion, hypercapnia does not occur until the pulmonary shunts reaches 50% [8]. Thus, given these physiological assumptions, in the course of CARDS, the onset of hypercapnia without severe hypoxemia is not admissible. On the other hand, patients suffering from neuromuscular diseases with respiratory muscles involvement, in the early phase of the development of hypoventilation, may exhibit mild hypercapnia associated with mild hypoxemia, as established by the alveolar gas equation [9]. Indeed, the assessment of the alveolar to arterial oxygen gradient (A-a gradient) would have been clinically useful in patients with hypoxemia of undetermined etiology, allowing to identify patients with an inappropriately elevated A-a gradient due to parenchymal diseases, and patients with A-a gradient

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within normal limits, who are affected by pure hypoventilation due to respiratory muscle weakness [9].

Finally, Rodrigues et al. correctly pointed out that in Murthy et al. [10] cases, the respiratory failure due to pulmonary complications of COVID-19 developed in elderly men with stable disease state or in pharmacological remission. Indeed, Murthy et al. [10] highlighted distinct differences between the two types of respiratory failure in subjects with MC and those occurring in stable MG patients. This distinction in our view is clinically crucial, having in mind that the two conditions, COVID-19 and MC, might overlap.

Declarations

Ethical approval None.

Conflict of interest None.

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