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Reply to respiratory failure due to neuro-COVID by Finsterer J et al

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To the Editor

We were pleased to receive the correspondence from colleagues [1] in relation to our review published in Journal of Clinical Neuroscience [2]. We are grateful to them for the chance to discuss some important issues.

As for the first point, we would like to clarify that the main purpose of our paper was to explore the pathophysiological events underlying respiratory failure in conditions clinically challenging for neurologists, such as myasthenia gravis (MG), Guillain Barre' syndrome (GBS) and other acute myopathies with or without rhabdomyolysis or chronic, as myotonic dystrophy (DM1) in the course of SARS-CoV-2 infection, to better handle and manage the acute respiratory distress (ARDS)due to SARS-COV-2 infection [2,3].

Indeed, SARS-COV-2 infection in patients with pre-existing neuromuscular disorders (NMD) could cause an unpredictable deterioration of the respiratory conditions, through an autoimmune mechanism or eventually by an acute exacerbation of a preexisting disease, leading to acute respiratory "pump failure", due to respiratory muscles weakness of different muscle groups, which have distinct effects on respiratory function [2]. We are aware that some evidences suggests that respiratory failure during COVID-19 may be caused by disturbance of any part of the neuro-ventilatory pump, including affection of the brainstem,such as encephalitis, stroke and GBS subtype brainstem Bickerstaff encephalitis, but we believe that these topics, although very interesting, are not the focus of our review and require a separate discussion.

Indeed,the derangement of the neuro-muscular coupling in the course of SARS-CoV-2 is very complex and not fully understood. Both autoptic and animal studies indicate that the brainstem is one of the primary central nervous system targets of SARS-CoV-2, and some authors raised the idea that brainstem involvement may add a neurogenic component to the respiratory failure, that occurs during COVID-19 [4]. However, the brain's respiratory and cardiovascular neuron circuits are closely intertwined in the brainstem and a brainstem dysfunction can cause a wide range of unpredictable clinical conditions. The ventral respiratory column in the medulla harbors the Bötzinger and pre-Bötzinger complexes, which are responsible of the control of the rhythming breathing, while the caudal ventrolateral medulla contains neurons responsible for controlling the heart rhythms [5]. Furthermore, in the brainstem, the nucleus tract solitaries and dorsal motor nucleus of the vagus, both play a role in the regulation of the motility and secretion of the gastrointestinal tract. Thus, brainstem disorders could result in a fatal cardio-respiratory failure, but also in a persistent low-grade dysfunction with mild/moderate respiratory, cardiovascular and gastrointestinal symptoms as previously hypothesized by some authors in the Long-COVID [6]. Given that, about 62 % of severe COVID-19 patients do not perceive dyspnea and the magnitude of the inspiratory effort is significantly lower, when compared to classical ARDS [7]. This condition, called "silent hypoxemia", despite still not fully understood, could be due to damage of sensory afferents in brainstem carrying signals from peripheral receptors [8]. Given the physiological complexity of the topics, we believe that it would be necessary to deal with this subject separately.

Second, there is evidence that infection by SARS-CoV-2 predispose to a prothrombotic state through different mechanisms, such as microvasculitis due to viral damage, angiotensin receptor-2 (ACE2) down-regulation, and disseminated intravascular coagulation [2]. Therefore, patients suffering from severe COVID-19 are at risk of respiratory failure due to pulmonary venous thromboembolism. Furthermore, cytokine storm and viral dissemination within the cardiomyocytes may result in cardiac injury and inotropic deficit, which can worsen and promote the respiratory pump failure in NMD patients through diaphragmatic hypoperfusion. However, in our review, we did not aim to discuss the risk of lung pulmonary embolism or the cardiac compromise during MG or Takotsubo syndrome (TS) associated myocartiditis, pericarditis and or TS as trigger of myasthenic crisis (MC) [9].

Third, Finsterer et al [1] proceed to state that the respiratory insufficiency could have been due to a myriad of other causes, including affection of the nerves innervating respiratory muscles or involvement of respiratory muscles during critically ill myopathy and neuropathy, occurring in intensive care Unit or during the course of small fiber neuropathy or chronic inflammatory polyradiculoneuropathy or multifocal motor neuropathy or as effect of number of drugs. We are well aware of these conditions, as noted in our discussion [2].

Fourth and most important point, Finsterer et al [1] among the drugs which might damage the muscle and nerves included corticosteroids (CS) and the interleukin-6 receptor blockade tocilizumab (TCZ). This assumption requires extreme caution. While it is true that high-dose CS, especially given intravenously, should be used with attention, as it can

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worsen weakness in as many as one-third of non-ventilated MG patients, oral CS are the gold standard therapy, recommended for patients with post-synaptic autoimmune disorders of the neuromuscular junction. In addition, the recent RECOVERY trial, a randomized controlled open label study [10] clearly showed that among hospitalized patients with COVID-19, the use of dexamethasone (at a dose of 6 mg once daily) resulted in significantly lower 28-day mortality than usual care in subjects who were receiving oxygen and mechanical ventilation (MV). Therefore, we should encourage the use of this treatment in cases falling into this category, until there is no other evidence from large randomized trials.

The same caution should be use in discussing about the use of TCZ, that in a large randomized trial [11] showed additional survival benefit in patients already treated with CS and the improvement of other clinical outcomes, such as reduced chances of requiring invasive MV and increased chances of successful hospital discharge.

Finally, one of the most important message of our review [2] was that the non-invasive assessment of respiratory muscles could be crucial to identify an acute development of respiratory muscle weakness in patients affected by severe COVID-19. This concept is not so trivial, because despite new technologies, such as ultrasound, have shown to be effective in the bedside identification of severe diaphragm dysfunction, these methods are still too seldom used by physicians. Therefore, even if our review cannot analyze all the complex mechanisms underlying ventilatory failure in the course of COVID-19, we believe that it could be of some help for physicians dealing with NMD and respiratory failure during the pandemic outbreak period. We conclude by quoting a famous writing by Lev Tolstoj, that we believe should always be kept in mind when seeking answers within complexity: “All ideas that have huge consequences are always simple ideas”.

Author contribution

GG: design, literature search, discussion, first and final draft, critical comments, final approval; AM: discussion, critical comments, final approval.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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