# Reply to: SARS-CoV-2 as a Potential Trigger of Neurodegenerative Diseases

We are excited that our article[1] has attracted the attention of other colleagues,[2] as we believe that given the current coronavirus diesease 2019 (COVID-19) pandemic it is essential to consider the potential long-term implications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. In particular, as Gomez-Pinedo and colleagues[3] point out, it is known that coronaviruses can be found in the central nervous system of elderly people and of patients with Alzheimer's disease, Parkinson's disease, or multiple sclerosis.

In the few months that SARS-CoV-2 has been storming the planet, our perception of the virus has evolved from a virus that causes a severe respiratory disease to a virus that can also severely impact the central nervous system and that may likely trigger long-term consequences we cannot fully anticipate. Part of the deadly capability of SARS-CoV-2 is its tight binding to the human angiotensin converting enzyme 2 receptor, with more than 20-fold higher affinity (~15 nM) compared with its predecessor SARS-CoV.[4,5] Interestingly, efforts to describe the mechanism of virus neutralization by antibodies have so far revealed that the antibodies bind the spike protein core, rather than the receptor binding domain.[6,7] These observations may open new avenues in treatment and vaccine development.[8]

As we wrote in Lippi and colleagues,[1] aging and several preexisting health conditions remain as the main risk factors for the severity of COVID-19. The common denominator to all these risk factors is the decreased performance of the immune system. Senescence of the immune system may shed light into the differences in COVID-19 adversity between young and old individuals as well as between men and women. For example, B lymphocyte depletion is characteristic of old age, affecting predominantly men.[9,10] Such changes in the immune system lead to "inflammaging," a term describing the presence of low-grade inflammation at an advanced age, also consistent with the gender bias of SARS-CoV-2.[11] The stronger age-dependent activation of the innate proinflammatory pathways in COVID-19 is observed in men,[9] which is consistent with a higher rate of inflammaging also among men.[12] Inflammaging may trigger the onset and contribute to the progression of age-related diseases, including those involving the central nervous system (eg, Alzheimer's disease).[13] Strikingly, in a very recent case report, the neuropathological analysis of the brain of a COVID-19 patient revealed a range of neuropathological lesions with features indicative of vascular and demyelinating alterations, consistent with parainfections processes affecting COVID-19 patients.[14]

Therefore, we believe it will be critical to implement programs to follow individuals who survived SARS-CoV-2 infections over time, and those countries who are capable of implementing such programs will be better equipped to provide the best care for their populations.

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