Reply to: "Parkinson's Disease and COVID-19: Do We Need to Be More Patient?"

In our paper, Lippi et al[1] speculated, early on, on the potential long-term implications of SARS-CoV-2 infections in the context of neurodegenerative disorders, such as Parkinson's disease (PD). After ~65 million infections and 1.5 million deaths, we are living unprecedented times. COVID-19 changed the way we live, and we are navigating by sight, much like many great explorers in the 15th century. At that time, many doubted the task they set out to do, and many reasoned for caution. In the end, a mix of caution and courage brought about opportunities, and discoveries changed the world forever. Poetry aside, we absolutely agree with Gonzalez-Latapi and colleagues[2] inasmuch only time and careful epidemiological studies will tell whether the long-term consequences of SARS-CoV-2 infection will increase the burden of PD. Although we and others innovated and raised potential implications of the infection, it was not our intention to create an exaggerated scare but, instead, to alert for the need to stay vigilant and prepared.[3,4]

In our paper, we drew parallels with other known connections between viral infections and neurological conditions, using the "Spanish flu" as an example. We understand the caution raised by Gonzalez-Latapi and colleagues and the fact that the causal effect of H1N1 infection and encephalitis lethargica is not consensual.[5] It is also true that only a few cases of post-SARS-CoV-2 infection parkinsonism have been reported thus far. However, we never speculated on a direct causal connection between COVID-19 and PD or any other neurodegenerative disorder and, therefore, we did not expect the large number of PD cases (10,000) put forward by Gonzalez-Latapi and colleagues. We consider that it is too early for calculations and estimations, and this is beyond the point of our initial publication.

We propose that a possible higher incidence of PD arising post-SARS-CoV-2 infection would be a phenotypic consequence of an increase in chronological age, both in intensity and in complexity. We suggest that COVID-19 may bring about an accelerated aging dimension whereby phenotypic consequences of aging, such as PD, might occur much earlier in life due to a sudden increase in the biological age of COVID-19 survivors.[6,7] For example, although in chronological time only 1 month has passed, in those who had COVID-19 the biological age of an individual may increase significantly, due to the severity of the disease in terms of inflammation.[3,8] With time, the biological age can regress up to a certain point in most individuals. However, in some individuals, age-related phenotypes may emerge or progress if organismal defenses fail.[7] Therefore, among the young population, such as in the cases described in Cohen et al and Faber et al,[9,10] the new-onset parkinsonism may have been related to a phenotypically silent predisposition to PD, which was revealed due to COVID-19. Moreover, among the elderly, this scenario renders them much more vulnerable to possible consequences of COVID-19 due to their more-advanced chronological age.[3,7] This vulnerability may be evident not only in the brain but also in other tissues, especially those more directly affected by COVID-19, like lungs or the gut.

In conclusion, and while we hope SARS-CoV-2 infections turn out to leave no long-term consequences in those infected, we maintain that countries that are capable of implementing programs to follow individuals who survived SARS-CoV-2 infections over time will be better equipped to provide the best care for their populations.

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