RESPONSE TO LETTER
TO THE EDITORS

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Response to the Letter to the Editors on the article reviewing the complex subject of 'Impact of SARS-CoV-2 on the nervous system'

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To the Editors

We are most grateful to Mehri et al. for their comments on the review we have prepared discussing the various impacts of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the nervous system [1, 2]. However, we would like to address a few minor limitations mentioned in their letter for the sake of clarification.

In the presented review, we set out the current state of knowledge on the particle of SARS-CoV-2, and we discussed what may have led to such a wide spread of the novel coronavirus. Most of the manuscript is dedicated to the various theories as to how the virus approaches the nervous system, and to discussing potential neuropathology mechanisms. The clinical impact of SARS-CoV-2 is further described, albeit to a lesser extent.

The first minor matter pointed out are the headings of section 7 and Table 2. We agree that the term "symptoms" does not fully reflect the content of these sections. Therefore, we suggest "symptoms and disorders" would be more appropriate.

The second limitation mentioned by Mehri et al. is an insufficient explanation of post-COVID disorders and the possible psychiatric sequelae of SARS-CoV-2 infection. We thank the letter's authors for their expansion of the list of possible post-infectious symptoms. We agree with most of them.

However, we cannot fully agree that either multiple sclerosis or myelin-oligodendrocyte glycoprotein associated disease are direct consequences of SARS-CoV-2 infection. There is no data supporting such a statement. These particular disorders are more likely to be triggered by an infectious agent, or their first manifestation may appear in post-infectious conditions.

Moreover, the potential of stimulating autoimmune activity is moderate in multiple sclerosis patients, as the relapse rate during the infection, and for several months after, has not yet proven to be higher [3]. Therefore, the neurological incidences following COVID-19 cannot be classified altogether, as they have been by the authors of the letter.

The pathomechanism behind such a broad presentation of neurological and psychiatric symptoms following COVID-19 is as yet unknown, and is probably multifactorial. However, some hypotheses have been presented. Persistent symptoms may be a consequence of numerous factors beyond the ones described in our review, e.g. a reduction in cerebrospinal fluid flow (reduced removal of brain metabolites); triggered and sustained neuroinflammation (activation of microglia, autoimmunisation, autoimmune mimicry); and impaired neurotransmission (e.g. GABAergic) [4].

Mehri et al. disagree with the impact of hypoxia on the central nervous system. However, they have focused only on direct damage to the CNS (seen in neuroimaging). Our review clearly states that the matter is much more complex, and that not only can acute hypoxia affect the CNS, but so also can prolonged oxygen deficit. A cascade of events may lead to indirect injury (e.g. injury to the blood-brain barrier) [5].

Furthermore, the authors claim that hypoxia does not explain peripheral damage to the nervous system, but it must be emphasised that several mechanisms lead to neurological deficits in SARS-CoV-2 infection. This matter is discussed in other sections of our review.

We did not state that hypoxia was the only factor causing neurological complications in COVID-19 patients.

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