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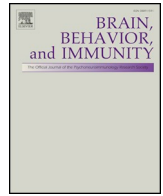
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Letter to the Editor

Potentially irreversible olfactory and gustatory impairments in COVID-19: Indolent vs. fulminant SARS-CoV-2 neuroinfection



To the Editor:

A recent study by Wu et al. (2020) discussed the neuroinvasive potential of SARS-CoV-2 on the premises of a lack of pathological evidence of definite CNS infiltration, and a predilection for what the authors termed as short-term effects on cerebral functions.

The authors' report is concise, and accurately identifies the scarcity of definitive laboratory evidence for SARS-CoV-2 CNS latency in the literature. There are, however, several aspects of SARS-CoV-2's neurotropism and its significance that are underrepresented in Wu et al.'s study. A general outline of these aspects is: (a) consistent SARS-CoV-2 neurotropism, determined by potentially irreversible hypogeusia and reversible hyposmia preceding the onset of respiratory symptoms, (b) the report of at least one case of fulminant CNS disease in the literature, defined by an encephalopathic syndrome associated with the exclusive detection of SARS-CoV-2 RNA in the patient's cerebrospinal fluid (CSF) and (c) selection bias in case definition of SARS-CoV-2 associated CNS manifestations.

Specifically, a recent multicenter study has identified frequent (i.e. more than 80% of the cohort) gustatory and olfactory impairments in included patients. Notably, while olfactory symptoms were mostly self-limiting, gustatory dysfunction persisted after the resolution of the respiratory symptoms in more than 70% of the patients (Lechien et al., 2020). Despite not being a constellation of symptoms exclusive to SARS-CoV-2 infection, hypogeusia and hyposmia are recurrent features of COVID-19 even in retrospective studies, where these symptoms were incidentally rather than systematically documented (Bénézit et al., 2020). These very studies support the concept of indolent SARS-CoV-2 neurotropism as part of COVID-19's natural history, with a nevertheless persistent and significant impairment to neuronal function.

Conversely, the case for fulminant neuroinfection is illustrated in the very first case report of SARS-CoV-2 associated encephalitis by Moriguchi and colleagues, where RT-PCR detected SARS-CoV-2 RNA in the patient's CSF, despite a lack of its detection in the nasopharyngeal swab specimen (Moriguchi et al., 2020).

In their study, Wu and colleagues correctly identify a gap of knowledge in our current understanding of SARS-CoV-2's interaction with neurons. The point they raise however also illustrates, by extent, the importance of recognizing mild manifestations of neurotropism in the clinical setting, such as gustatory and olfactory impairment. This point is further exemplified in the studies of Lechien et al. (2020) and Bénézit et al. (2020), where hypogeusia and hyposmia were detected

below at 5% retrospectively and more than 80% of the respective cohorts prospectively. In a similar manner, Moriguchi et al.'s (2020) case report indicates that even a fulminant SARS-CoV-2 neuroinfection may escape current case definitions. Taken together, these reports point toward a needed paradigm shift in study design, in order to properly document and phenotype the extent of SARS-CoV-2's neuroinvasive potential, as well as its possible future consequences.

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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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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2020.04.071>.

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