Sowing SARS-CoV-2 to reap neurodegeneration: A hamster study

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The jury is still out on how widespread brain infection by SARS-CoV-2 is, and what invasion route or routes the virus takes. However, more and more reports suggest that even patients who contract mild forms of COVID-19 suffer from long-term mental health and neurological sequels (see for example, a very recent study [1]). In this issue of *eBioMedicine*, Käufer et al. show in a Golden Syrian hamster model of COVID-19 that SARS-CoV-2 infection, despite largely sparing the brain, leads to an increase in microgliosis and an accumulation of hyperphosphorylated Tau and alpha-synuclein proteins in distant brain regions that persist post-infection.[2] The interest of this study is two-fold: (i) it is conducted in an animal model whose ACE2 protein naturally binds most strains of SARS-CoV-2, unlike mice, and which mimics various aspects of COVID-19 pathogenesis in humans, including sub-lethal infection and recovery; and (ii) it suggests that even in the absence of overt neuroinvasion by SARS-CoV-2, viral infection in the nose can trigger neuroinflammation and neurodegenerative changes in the brain that persist at least into the medium term, possibly setting the stage for the increased long-term incidence of disorders such as Alzheimer's or Parkinson's disease.

That SARS-CoV-2 infects brain cells, including neurons, in human patients is now amply evident from post mortem studies. However, these patients, by definition, had lethal infections that may have facilitated access to the brain or broken down protective barriers. Whether the virus also infects brain cells in COVID-19 patients who survive mild or moderate disease can only be inferred from the symptoms and clinical signs displayed by these patients, and from sublethal infections in preclinical models.[3] Similarly, although the olfactory route into the brain of humans seems self-evident given the abundance of SARS-CoV-2 in the upper respiratory tract, there are as many studies showing that the virus infects olfactory sensory neurons as those stating the contrary, giving rise to other hypothetical pathways for the virus to enter the brain, such as along the nervus terminalis or the hypothalamus (reviewed in[4]). In addition, the extensive destruction of brain endothelial cells by the SARS-CoV-2 main protease in both patients and animal models, including hamsters, suggests that the brain may indeed be bathing in a pool of blood-borne virus particles.[5] Moreover, in contradiction to the current article, even neurons of the olfactory bulb of hamsters have been shown by others to be infected by SARS-CoV-2 after nasal administration, and to contribute to viral pathogenesis.[6] In this context, it is a pity that the current article does not provide images of immunolabeling for viral proteins in the olfactory bulb and other brain areas, that only one antibody and one acute time point were used to determine viral presence or absence in the brain, and that the methods do not mention how and in what brain regions viral titers were measured by plaque forming assays.

Regardless of whether neuroinvasion was really absent or merely undetectable, the fact that SARS-CoV-2 infection triggered neuroinflammation in the olfactory bulb and increased hyperphosphorylated Tau and alpha-synuclein levels in the suprahippocampal cortex, distant from the site of viral administration, and that these changes persisted beyond the infection period, is interesting. These results are reminiscent of those from an almost concurrent study in rhesus and cynomolgus macaques, demonstrating the persistence of microgliosis and alpha-synuclein aggregation several weeks after SARS-CoV-2 infection.[7] The link between viral infections, inflammation and the risk of developing neurodegenerative disorders has been postulated for decades, and has been a major concern since the beginning of the pandemic,[8] and indeed, findings from both living COVID-19 patients and post mortem tissues confirm the presence of changes mimicking an acceleration of neurodegenerative processes that usually take years to manifest. However, whether these changes are an acute reaction to infection and/or death, or whether they represent the seeds of a long-term breakdown in the sequestration or clearance of pathogenic molecules by the brain remains to be determined. In addition, a number of different molecular pathways that are implicated in neurodegenerative processes appear to be triggered by SARS-CoV-2 infection (see for example[9,10]). Both

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mechanistic studies, including in other animal and cellular models, in order to further elucidate these pathways and their interactions, and prospective studies in human COVID-19 patient cohorts, in order to validate the relevance of a given pathway in the development of neurodegenerative disorders and functional deficits in the long run, are required.

To conclude, while SARS-CoV-2 infection may be transient in itself, the incidence of long-term neurological and mental health consequences in a significant proportion of patients is worrying. By bringing to light neuroinflammatory and neurodegenerative changes in the hamster brain that persist beyond the infectious phase, Käufer et al.[2] add another piece to the puzzle of SARS-CoV-2's effects on the brain, necessary to evaluate the risk of a second pandemic of accelerated neurodegeneration and cognitive deficits.

Declaration of interests

The authors have no potential conflict of interest to report.

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