Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Identifying those at risk for COVID-19 related suicide. Response to "Hyper/neuroinflammation in COVID-19 and suicide etiopathogenesis: Hypothesis for a nefarious collision?"

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Regarding the interesting paper in this Journal (https://doi.org/10.1016/j.neubiorev.2022.104606), Costanza and coauthors mentioned the increase in suicidal ideation and suicidal behavior reported during the initial phase of the Coronavirus Disease 2019 (COVID-19) pandemic and that it possibly was related to various psychosocial factors and pre-existing psychiatric illness, while the increase in suicide risk seen during later phases of the pandemic was fueled by a pathological hyper-inflammatory state, initiated by the virus causing COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As such, SARS-CoV-2 activated macrophages and mast cells in the periphery and macrophages and glial cells in the brain release a myriad of inflammatory factors including IL1, IL6, and TNFα. Moreover, the authors pointed out that a similar inflammatory signature has been associated with suicide risk and posited that neuroinflammation from COVID-19 is overlapped with that of suicide pathophysiology. However, can we better identify those at higher risk for COVID-19 associated suicide?

The apolipoprotein E4 (apoE4) genotype is an established risk factor for Alzheimer's disease and recent UK Biobank data has shown it to be associated with an increased risk for severe COVID-19 (Kuo et al., 2020). ApoE, a protein involved in lipid metabolism in the periphery and brain, exists in three major isoforms (apoE2, apoE3, and apoE4), giving rise to three heterozygous and three homozygous phenotypes; the apoE3/4, apoE4/4, and E3/E3 phenotypes occur in about 25–30%, 2–3%, and 65–70% of the population respectively. Specifically, the apoE4/4 genotype was associated with a more than 2-fold increase in severe COVID-19 in hospitalized patients. It is noteworthy that apoE is expressed in astrocytes and neurons, and a study using human induced pluripotent stem cell (hiPSC) models found that SARS-CoA-2 readily infects astrocytes, neurons and brain organoids. Moreover, apoE4/4 compared to apoE3/3 hiPCS astrocytes exhibited an enhanced cellular response to SARS-CoA-2 (Wang et al., 2021). Consequently, this study bolstered the observation that the apoE4 genotype is a risk factor for severe COVID-19 outcomes and the neurotropism of SARS-CoA-2 is more potent in those carrying that genotype.

Furthermore, the neurotropism of SARS-CoA-2 was exemplified on analysis of longitudinal neuropsychologic and MRI data from 785 subjects in the UK Biobank aged 51–81 years (Douaud et al., 2022). The participants of the study had two brain MRIs separated by 3.2 years. During that time 401 subjects tested positive for SARS-CoV-2 and the remaining 384 were negative for the virus and thus served as the control group. Nearly all those testing positive were not hospitalized; therefore, the study basically investigated the effects of mild COVID-19. On longitudinal analysis, the group testing positive for the virus compared to the control group exhibited several adverse effects, which included greater loss of grey matter thickness and tissue contrast in the parahippocampal and orbitofrontal gyri, evidence of tissue injury in areas functionally connected to the primary olfactory cortex, greater overall reduction in brain size, and greater cognitive decline. Since the olfactory

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epithelium is extremely susceptible to SARS-CoV-2 infection, it is not surprising that most patients during the subacute stage of the viral infection exhibit impairments of taste and smell. In sum, this study suggests that neurotropic SARS-CoV-2 spreads in part through olfactory pathways, which leads to neuroinflammation and brain degeneration.

Notably, air pollution is a risk factor for neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD), and olfactory pathways are involved. To this point, a study of 179 consecutive autopsies of children and young adults of sudden death not involving the brain, in Metropolitan Mexico City (an urban polluted environment) before the COVID-19 pandemic, revealed that chronic exposure to elevated levels of air pollution resulted in AD and PD pathology in the olfactory bulbs of the children and young adults aged 11 months to 40 years (Calderón-Garcidueñas et al., 2018). Moreover, apoE4 versus apoE3 carriers were roughly 10-fold more likely to show olfactory bulb AD and PD pathologies. Strikingly, young adults who were apoE4 carriers had a nearly 5-fold risk of suicide. Consequently, this study suggests that neurodegenerative diseases such as AD and PD can have origins early in life in part from chronic exposure to high levels of air pollution, the olfactory pathways (particularly in apoE4 carriers) are involved in the pathogenesis, and apoE4 carriers are possibly more susceptible to the deleterious effects of neuroinflammation, including suicide.

In conclusion, emerging evidence suggests that the apoE4 genotype may confer an increased risk of COVID-19 related suicide as a result of neuroinflammation and the olfactory pathways provide a conduit for SARS-CoV-2 to enter the central nervous system and lead to the neuroinflammation. Conceivably, individuals diagnosed with 'long-haul COVID' and/or recurrent COVID-19 infections may exhibit an even more robust and prolonged neuroinflammatory response (Mehandru and Merad, 2022). Furthermore, it is plausible that those residing in polluted urban areas and carrying the apoE4 genotype are particularly sensitive to COVID-19 related suicide. Notably, the apoE genotype can be easily determined by a buccal swab or blood test. Finally, studies from various locations have shown that *trace* doses of lithium in drinking water are associated with significant decreases in suicides and homicides and elemental lithium taken in *trace* amounts (1 mg daily) is safe and inexpensive (Goldstein and Mascitelli, 2016). As such, *trace* doses of lithium may decrease COVID-19 related suicide, particularly among individuals carrying the apoE4 genotype and living in urban areas – this needs investigation.

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