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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doi: 10.1016/j.bja.2021.06.002
Advance Access Publication Date: 8 June 2021

COVID-19: a novel risk factor for perioperative neurocognitive disorders

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Keywords: COVID-19; older patients; perioperative neurocognitive disorders; risk factor; SARS-CoV-2

Editor—Older patients with current or previous SARS-CoV-2 infection (COVID-19) have been undergoing surgical interventions at an increasing rate during the COVID-19 pandemic and face a high risk of postoperative complications. Most older patients are expected to recover from acute postoperative complications, including most pulmonary and renal complications and delirium. Recently, a national database study on hip fracture characteristics and outcomes during the COVID-19 pandemic in the USA showed that older patients with hip fracture and concomitant COVID-19 experienced significantly higher rates of acute postoperative complications, especially pulmonary complications (22.9%).[1] However, long-term neurological sequelae, such as perioperative neurocognitive disorders (PNDs), commonly occurring in older patients after major noncardiac surgery (incidence as high as 40%),[2,3] have received relatively little attention.

PNDs that encompass acute postoperative delirium and longer-lasting postoperative cognitive dysfunction are age-related neurological disorders and are associated with dementia.[4] Older patients with a PND have a significantly increased mortality 3 months after surgery and are at risk for a higher rate of disability, leading to loss of employment, which may lead to a greater reliance on social security.[5] Interestingly, the enhanced expression of angiotensin-converting enzyme-2 (ACE-2) receptors in the CNS of patients with dementia may make them more susceptible to COVID-19 (Fig. 1).[6,7] Clinical studies have identified advanced age, major surgery, low educational level, history of alcohol or opioid use, anticholinergic medication, and pre-existing cognitive impairment as important risk factors for PND.[3,8] The COVID-19 pandemic has significantly affected the epidemiological characteristics of many diseases, and COVID-19 must be considered a potential risk factor for acute or chronic neurological complications because the causative virus, SARS-CoV-2, is more invasive in the CNS than other coronaviruses.[9,10] Acute neurological symptoms associated with COVID-19, including confusion, headache, hypogeusia, hyposmia, and seizures, provide evidence of direct invasion by SARS-CoV-2 into the CNS. Most patients with COVID-19 fully resolve from these acute symptoms after clinical recovery.[7] However, a small observational study showed that 33% of patients with severe COVID-19 experienced cognitive and motor dysfunction, including inattention, disorientation, and poorly organised movements in response to command, even after hospital discharge.[11] Long-term neurological disorders have been observed in non-critical patients with COVID-19 as well, although results are yet to be completed.[12] Moreover, COVID-19 may promote the initiation and progression of age-related progressive neurodegenerative conditions, such as Alzheimer's disease (AD). Preliminary observations have revealed that COVID-19 causes worsening of behavioural symptoms and potential gradual aggravation of the underlying AD neuropathologies and related dementia, which may take months or years to detect.[13–15] Support for a relationship between age-related neurodegenerative conditions and COVID-19 has yet to be reported because of the recent origin of the pandemic.

Anaesthesia and surgery can disrupt the integrity of the blood–brain barrier (BBB) and facilitate migration of peripheral innate immune molecules into the hippocampus, and SARS-CoV-2 infection may accelerate this process.[16,17] Neurotoxicity via ACE-2 receptors in the hippocampus can be caused by SARS-CoV-2 via its access to the CNS through retrograde axonal transport along the olfactory bulb or disrupted BBB (Fig. 1).[7,9] SARS-CoV-2-mediated immune responses can also play a critical role in cognitive impairment through indirect CNS involvement. Furthermore, the molecular mechanisms, including significant neuroinflammation, mitochondrial oxidative stress, and accumulation of amyloid beta (Aβ), of SARS-CoV-2-induced cognitive disorders are similar to those of PNDs (Fig. 1).[7,8] Surgical trauma can trigger complement signalling activation in the CNS and subsequently activate microglia via CD11b signalling, which further increases SARS-CoV-2-mediated neuroinflammation.[9,18] A recent editorial suggested a correlation between PND and cognitive disorders associated with SARS-CoV-2 because of their overlapping inflammatory response to injury.[12] The authors stated that it may be beneficial to alleviate long-term neurological consequences of COVID-19 by implementing preventive interventions or treatments before surgery and anaesthesia, which could improve pre-existing poor cognitive and functional outcomes for patients with COVID-19.

Increasing evidence suggests that mitochondrial dysfunction is involved in both PND and COVID-19.[8,19] SARS-CoV-2 can enter cells via the ACE-2 receptor and affect mitochondria,

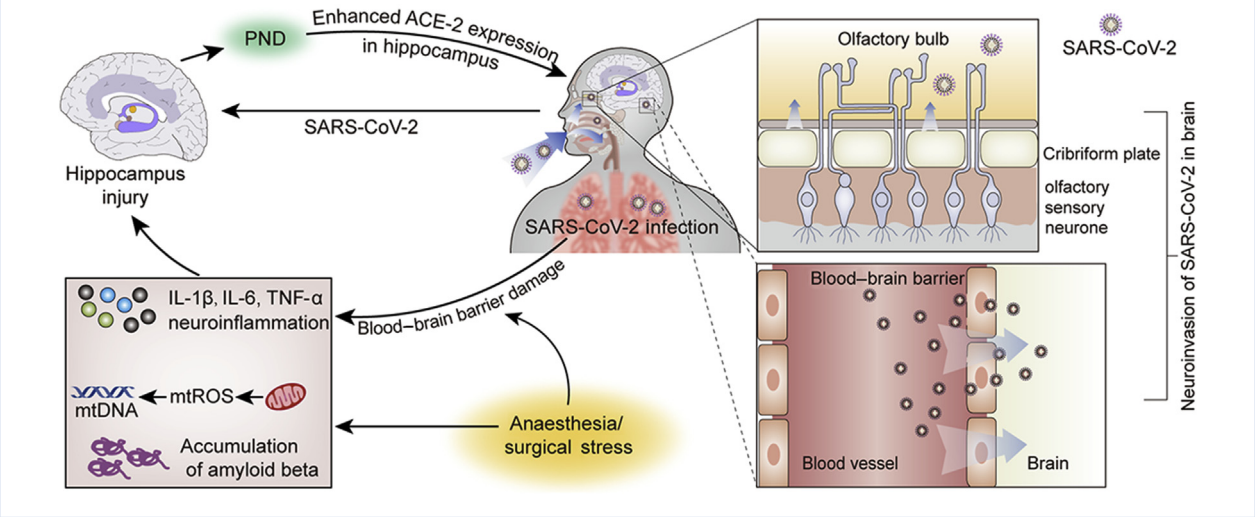

Fig 1. Mechanism of neuroinvasion by SARS-CoV-2 and the potential association between SARS-CoV-2 infection, anaesthesia and surgery, and PND in cognitive impairment. Neuroinvasion by SARS-CoV-2 occurs through retrograde axonal transport along the olfactory bulb or disrupted blood–brain barrier. SARS-CoV-2 infection combined with anaesthesia and surgery may lead to significant neuroinflammation, excess mtROS, and amyloid-beta accumulation that can cause hippocampus injury. Furthermore, PND may lead to enhanced ACE-2 expression in the hippocampus, making it more susceptible to SARS-CoV-2 infection. ACE-2, angiotensin-converting enzyme-2; IL-1β, interleukin-1β; IL-6, interleukin-6; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; PND, perioperative neurocognitive disorder; TNF-α, tumour necrosis factor-α.

causing increased fusion and excess production of reactive oxygen species, thereby damaging mitochondrial DNA and accelerating CNS oxidative stress.[19] Additionally, reports have suggested a critical role of Aβ accumulation in the brain in PND.[20] SARS-CoV-2 neuroinvasion could promote endothelial dysfunction and loss of pericytes (disrupted BBB), which can impair Aβ clearance and lead to excess Aβ generation in the hippocampus.[7,16] SARS-CoV-2 infection could directly induce Aβ generation in the CNS as part of the immune response; however, this hypothesis needs to be tested further.[7]

Taken together, COVID-19 may potentially lead to an accelerated cognitive decline associated with anaesthesia and surgical stress through independent and synergistic mechanisms. COVID-19 soon could be recognised as a long-term risk factor for accelerated onset or deterioration of PND in the ageing population undergoing surgery. Future clinical research needs to consider COVID-19 as a potential risk factor for PND in the post-COVID-19 era. Long-term prospective longitudinal studies in older patients undergoing surgery and anaesthesia with concomitant or previous COVID-19 diagnosis should be designed to determine the effect of COVID-19 on the pathological progression of PND and other age-related dementias.

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

Natural Science Foundation of Shandong Province (ZR2020QH291 and ZR2020MH126); Key Research and Development Plan of Shandong Province (2019GSF108228); Qingdao Key Health Discipline Development Fund (2019); Qingdao Outstanding Health Professional Development Fund (2019); Scientific Research Foundation of Qilu Hospital of Shandong University (Qingdao), China (QDKY2018QN12 and QDKY2019YC06).

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doi: 10.1016/j.bja.2021.06.016
Advance Access Publication Date: 19 June 2021