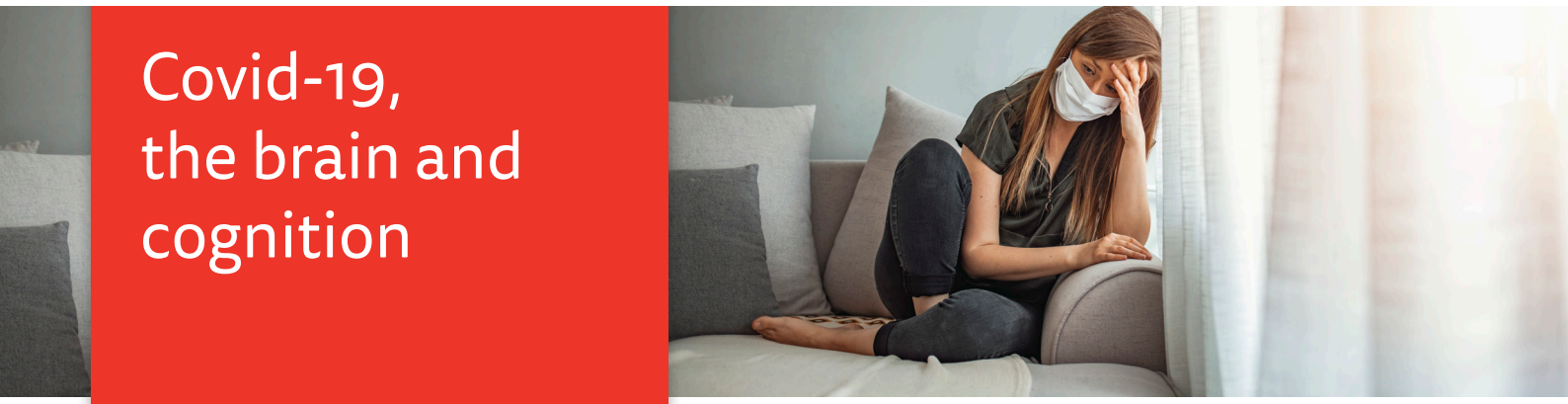
Covid-19, the brain and cognition



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The word 'unprecedented' has perhaps never been used as frequently as it has over the past 15 months. Remarkably, given the acute life-or-death exigencies of the Covid-19 pandemic, several research groups at major centres around the world have already developed working parties to investigate the broader impact of the disease. In particular, some early findings have already started to emerge concerning the impact of Covid-19 on the neuraxis.

In the early months of the COVID-19 pandemic, clinicians struggled to keep patients breathing, and focused mainly on treating damage to the lungs and circulatory system. But even then, evidence for neurological effects was accumulating. Some patients hospitalized with COVID-19 were experiencing delirium: they were confused, disorientated and agitated[1]. In April 2020, a group in Japan published the first report of someone with COVID-19 who manifested swelling and inflammation in brain tissues[2]. Another clinical report described a patient with deterioration of myelin[3], the fatty coating that is essential for the functioning of neurons.

The prevalence of neurological problems in Covid-19 has remained an open question since early single case and small group reports; however, it has become apparent that neurological problems are not rare[4]. In terms of underlying mechanisms, although viruses can invade and directly infect the brain, it is not yet clear whether SARS-CoV-2 does so to a significant extent. Indeed, rather than being due to infection of brain cells *per se*, neurological features could be a result of alternative mechanisms (e.g. overstimulation of the immune system). Indeed, neurological outcomes have been suggested to be both indirect (as a result of thrombotic complication, inflammatory consequences, hypoxia, blood pressure dysregulation) and/or direct (neurotropic properties of the virus). The current documented range of brain-related sequelae include stroke, brain haemorrhage and delirium. Specifically, strokes (caused by clots migrating to the brain) have been reported in COVID-19 patients of all ages, despite relatively mild respiratory signs in at least some of these cases[5]. It is likely that there are several different disease processes at work in terms of the neurological impact of Covid, with multiple neuroinvasive pathways proposed[6].

In terms of broader mechanisms, COVID-19 patients may be impacted cognitively (and perhaps also in terms of their mental health) due to post intensive care syndrome (PICS), plausibly linked to underlying inflammatory processes ('cytokine storm')[7]. Indeed, one pre-COVID-19 study found 20%-40% of ICU patients experienced delirium, with rates climbing to 60%-80% for patients on ventilators[8]; these outcomes are thought to be related both to i) severe illness and ii) intensive care treatment.

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With respect to the major published findings that have appeared in the literature in larger cohorts, an early study published by Ellul et al. at the University of Liverpool (UK) reported a range of neurological manifestations among 901 COVID-19 patients, including loss of smell/taste and confusion[9]. Additionally, Helms et al. reported 58 cases in France with 'neurological findings' in 67% of patients[10], while in the Johns Hopkins group Fotuhi et al. reviewed the neurological sequelae of COVID-19 in patients presenting with acute neurological symptoms (e.g. stroke) even without typical respiratory symptoms (such as fever, cough, or shortness of breath)[11]. Indeed, it may reasonably be expected that the sicker patients are the more neurological issues they have. However, this does not appear necessarily to be the case. A UK study published by the National Hospital (London) COVID-19 Study Group (describing findings from 43 patients with severe neurological complications from COVID-19[12]) reported that some patients with relatively mild respiratory symptoms manifested severe neurological symptoms. Five major neurological diagnostic categories emerged in this subgroup: encephalopathies, inflammatory CNS syndromes (acute disseminated encephalomyelitis, encephalitis and isolated myelitis), ischaemic strokes, peripheral neurological disorders and 'miscellaneous central disorders'.

A scoping review published by Wenting et al.[13] sought to summarize the published literature on neurological manifestations of COVID-19. While no extant articles were identified in this review regarding cognitive consequences in COVID-19 patients *per se*, there were widespread reports of neurological manifestations and/or underlying CNS mechanisms. Findings varied from relatively mild outcomes (e.g. loss of taste and smell, dizziness, headache) to more severe effects (e.g. ischaemic stroke, encephalitis).

Subsequent published studies have reported that neurologic manifestations may be frequent in COVID-19, including with respect to cognitive impairment[14].

Indeed, in the context of what has been termed 'long' Covid, affected patients may be at higher risk of developing cognitive decline even after overcoming the primary COVID-19 infection[15]. Social cognition and interpersonal functions may also be adversely impacted[16].

With respect to treatment, as per the Stanford Hall consensus statement for post-COVID-19 rehabilitation[17], cognitive input is likely to be important for recovering patients in the context of multidisciplinary rehabilitation for combination of physical, cognitive and emotional issues[18].

FUTURE DIRECTIONS

Early recognition, investigation and management of COVID-19-related neurological disease is challenging. The first step is to document what symptoms occur, how frequently and which treatments benefit neurological, cognitive and psychiatric outcomes. Researchers across the globe have registered with the Global Consortium to Study Neurological Dysfunction in COVID-19, collecting data and evaluating functional and cognitive outcomes to inform treatment strategies[19]. However, to date trials of antivirals and other therapies being tested to treat COVID-19 are using fairly coarse outcome measures - such as survival or duration of hospitalization. Notwithstanding successfully vaccination initiatives now taking place internationally, it is important that potential treatments are also tested promptly in affected patients; some of the brain damage from COVID-19 may be irreversible.

The picture is still evolving. Further clinical, neuroradiological, biomarker and neuropathological studies are essential to determine the underlying biological mechanisms in order to guide treatment. Longitudinal follow-up studies will be necessary to ascertain the long-term neurological (including neuropsychological) consequences of the pandemic.

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