Scientific Commentary

The cognitive aftermath of COVID-19

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During the last five centuries our humanity has experienced a pandemic on average every 36 years (Taubenberger *et al*., 2019). Currently, the entire world is being challenged by a pandemic due to the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and health systems are struggling to identify potential infected people to reduce the propagation and the impact of the coronavirus disease 2019 (COVID-19). The acute respiratory distress syndrome (ARDS) associated with the infection by SARS-CoV-2 is the main cause of hospitalisation and mortality in patients with COVID-19. However, growing evidence based on case-reports and retrospective observational studies (Zhou *et al*., 2020; Mao *et al.*, 2020) indicates that COVID-19 also involves organs outside the respiratory system.

In previous epidemics by other human coronaviruses, both central and peripheral neurological manifestations were reported (Umapati *et al.*, 2014; Arabi *et al.*,2015; Gu J *et al.*, 2005), indicating a potential neurotropism. COVID-19 has already affected a larger number of people than previous coronavirus epidemics, and it could be anticipated that a proportion of these patients will suffer acute and/or chronic neurological consequences. There is growing literature indicating that COVID-19 may be associated with acute cerebrovascular disease (Zhou *et al.*, 2020; Oxley *et al.*, 2020), necrotizing encephalopathy (Poyiadji N *et al*., 2020), or Guillain-Barré syndrome (Zhao *et al.*, 2020), among others. However, since infection by SARS-CoV-2 can proceed without symptoms, the causality in these reports remains unproven.

A poorly described aspect of COVID-19 is whether cognitive function is affected, directly or indirectly, by the SARS-CoV-2 infection. Patients with ARDS of any cause experience a high prevalence of cognitive impairment, and up to 20% of them show long-term deficits (Sasannejad *et al*., 2019). Typically, individuals who survive ARDS demonstrate deficits in executive functions and short-term memory, and increased rates of anxiety and depression. Risk factors for long-term cognitive impairment after ARDS include a combination of pathophysiological events, medical complications and interventions and pre-existing conditions. In the case of ARDS due to SARS-CoV-2, severe hypoxia

and cytokine-mediated damage are cardinal biological factors that may lead to brain damage and cognitive impairment.

The extreme levels of pro-inflammatory cytokines observed in COVID-19 patients are likely to induce neurotoxicity. The high production of cytokines TNF-α, IL-6, IL-1α and IL-1β can cause “sickness behaviour”, a syndrome that includes impaired concentration, reduced motivation, motor slowing and depressive symptoms (Dantzer *et al*., 2008). It is known that the brain monitors peripheral innate immune responses by several pathways that act in parallel, that ultimately lead to the production of pro-inflammatory cytokines by microglia. In turn, cytokines will act on several brain circuits via cytokine receptors or intermediates, such as prostaglandins E2. One of the pro-inflammatory cytokines involved in the COVID-19 is IL-6, which is known to contribute to the expression of brain cytokines during infections (Sparkman *et al*., 2006). A small and uncontrolled trial with tocilizumab (Xu *et al*., 2020), an anti-human IL-6 receptor monoclonal antibody, in patients with severe COVID-19 showed improvement in clinical outcome and in the inflammatory responses. It will be important to elucidate if anti-IL-6 treatments used in severe cases of COVID-19 ARDS will show benefit in reducing future cognitive impairment or depressive symptoms. Additional contributing factors to cognitive impairment may be sepsis, sedating and anaesthetic drugs, and mechanical ventilation. Furthermore, it is expected that, as in non-COVID ARDS (Sasannejad *et al*., 2019), pre-existing cognitive impairment or delirium during the admission will increase the likelihood of more severe cognitive decline. In patients infected by SARS-CoV-2 admitted with respiratory symptoms, we have observed common confusion in otherwise cognitively healthy patients and rapid decline in patients with previous cognitive impairment. It is still early to conclude whether these cognitive symptoms are proportional to the degree of hypoxia or these are more common than in other non-COVID ARDS.

In addition, the psychological effects of long confinement periods, social isolation and traumatic personal or familiar experiences associated to the disease will have to be taken into account when evaluating the potential cognitive effects in patients with COVID-19 or even in people not infected by SARS-CoV-2 but with pre-existing cognitive impairment or dementia.

In the paper by Ritchie *et al*., the authors review in detail the potential cognitive consequences of COVID-19. The authors propose three mechanisms to explain cognitive dysfunction during the infection by SARS-CoV-2: 1) direct central nervous system (CNS) damage induced by the virus 2) non-CNS complications that affect the brain and 3) psychological distress due to social isolation and a severe medical illness. The authors stress the need to investigate in detail the potential underlying mechanisms of cognitive impairment of COVID-19, as well as potential therapeutic strategies. As the authors state, unfortunately, coronavirus outbreaks have been common in the last decade and more could come in the future.

It remains to be seen whether the current COVID-19 pandemics will lead to an increase in neurological consultations due to cognitive complaints in the upcoming months, but clinicians should be alert of this potential effect. In addition, neurologists should evaluate the potential effects of COVID-19 on patients with pre-existing cognitive impairment. Formal neuropsychological evaluations, biochemical or neuroimaging biomarkers could be useful in assessing the extent and progression of neurological symptoms in patients with COVID-19.

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