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On the plausibility of late neuropsychiatric manifestations associated with the COVID-19 pandemic

Dear Sir

Recognition of the association between acute and subacute different *neuropsychiatric manifestations* with the infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the ongoing coronavirus disease 2019 (COVID-19) pandemic, is progressively being recognized [1]. *The potential emergence of late onset neuropsychiatric manifestations after infection with* SARS-CoV-2 remains to be discussed. After the "Spanish" influenza pandemic in the 20th century, an outbreak of encephalitis lethargica (EL) [2], a neuropsychiatric disorder of possible autoimmune origin emerged occurring soon after the acute phase or at some time later [3]. It's worthwhile to highlight that manifestations of EL such as sleep disturbance, fatigue, psychosis, catatonia, movement disorders among others were identified in previous historical epidemics since the 15th century [3]. Molecular mimicry leading to damage of the brainstem respiratory pace-maker [4] and occurrence of neurological autoimmune disorders after SARS-CoV-2 infection (Gillian Barré syndrome and its variants) [5,6] are indicative of the potential inducer of autoimmunity involving the nervous system on the long-term.

Apart from a single study showing an association of seropositivity for specific coronavirus (HCoV-NL63) with chronic mood disorder [7], nothing is known about the possibility of late *neuropsychiatric manifestations associated with coronavirus infections.*

The is indirect evidence (Fig. 1) supporting the biological pathophysiology of late occurrence of *neuropsychiatric manifestations after* SARS-CoV-2 infection.

Proinflammatory cytokines such as the interleukin-6 (IL-6) [8] or tumour necrosis factor alpha (*TNF-α)*[9] are associated with development of late *onset neuropsychiatric manifestations*. COVID-19 is associated with systemic inflammatory storm with a massive release of cytokines, chemokines, including IL-6 and *TNF-α*[10]. Delirium it's not rare in patients with COVID-19 [1], suggesting that at least acutely, significant break of blood brain barrier and neuroinflammation occurs. Latent viral chronic brain infection caused by viruses, per example the human herpes virus 6 infections or the measle virus are associated with late cognitive and behaviour disturbances [9,10]. In murine models, coronaviruses can invade the brain and cause chronic infection [11,12]. The presence of coronavirus was demonstrated in the brain tissue in a single patient after SARS-CoV infection [13]. Very low levels of SARS-CoV-2 was detected in very few patients who died from COVID-19 [14]. Despite the inexistence of documented cases of 2019-nCoV chronic brain infection, the invasiveness and neurotropism of the virus [15],obliges to leave this possibility open.

SARS-CoV-2 is worldwide distributed and affecting people with different genetic background. The virus itself, is also genetically adapting to humans [16]. Hence, in the context of an infinitude of virus-host interactions, the possibility of *late neuropsychiatric manifestations after* SARS-CoV-2 infection should be considered. Careful monitoring of chronic or *late neuropsychiatric manifestations is important to uncover mechanisms of the disease and guide interventions to prevent. Most patients with* SARS-CoV-2 infection are asymptomatic and the *durability of serological markers of* infection is unknow. This might preclude studies based on serological status. Due to the large variability of SARS-CoV-2 infection prevalence between sites, ecological studies might be a promising design to address patterns of occurrence of *late neuropsychiatric manifestations.*

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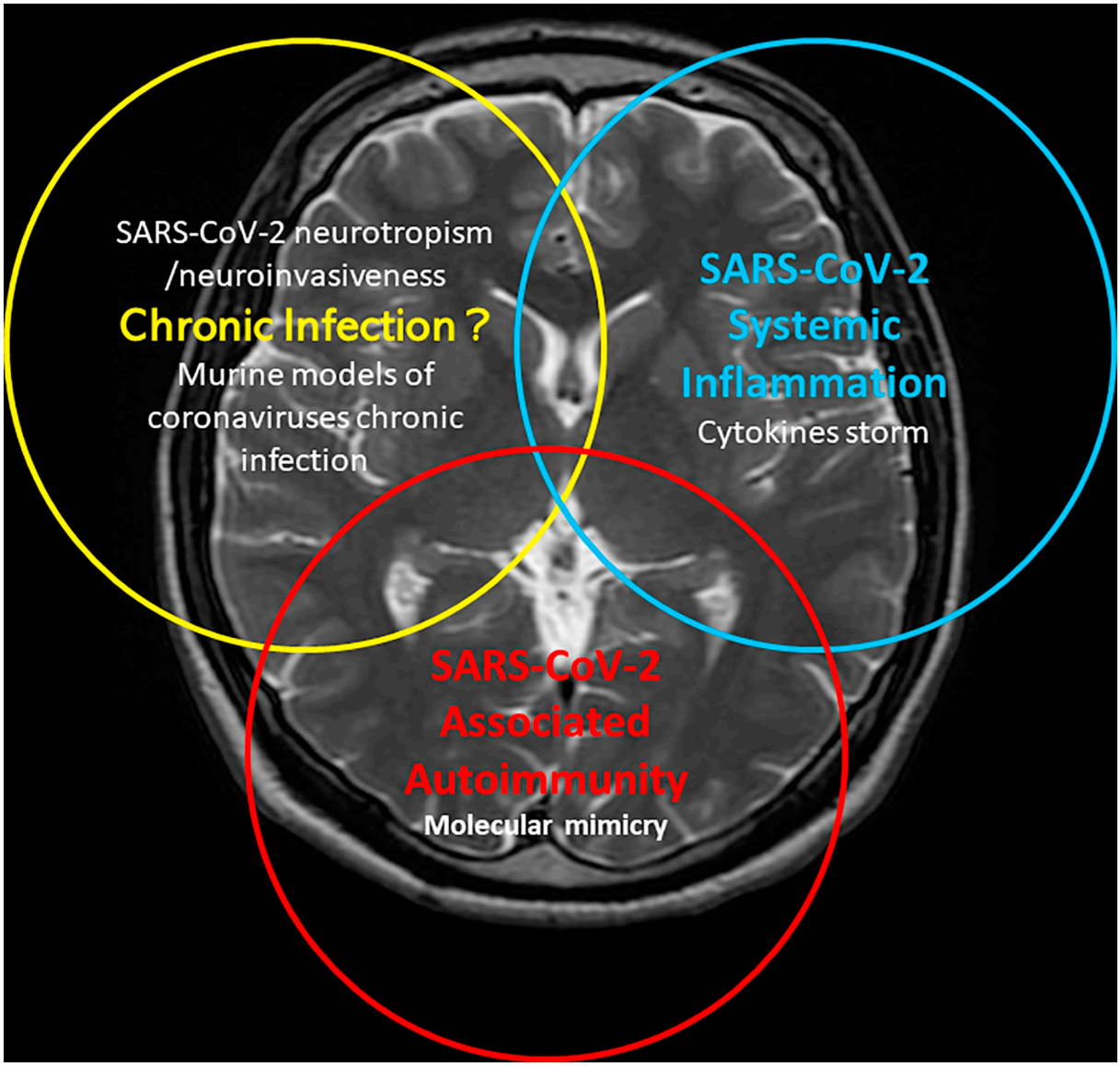

Fig. 1. Schematic representation of potential mechanisms involved in the occurrence of late neuropsychiatric complications.

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