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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Letter to the Editor

Putative mechanisms explaining neuro-COVID

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With interest we read the article by Kayhanian et al. about the presumed neuro-immunological mechanisms underlying the involvement of the central nervous system (CNS) and the peripheral nervous system (PNS) (neuro-COVID), about the neuro-immunological responses to the viral infection, and about the therapeutic approaches for neuro-COVID (Keyhanian et al., 2020). Proposed mechanisms explaining neuro-COVID were direct attack of the virus, neuro-inflammation, autoimmune responses to the infection, hypercoagulability, metabolic injury, or hypoxic injury (Keyhanian et al., 2020). Treatment relies on targeting the virus (antivirals, neutralizing antibodies, convalescent plasma therapy), targeting the inflammatory response (immune-modulatory medications, cytokine inhibitors), and on vaccines (put in promising by BionTech, Moderna, AstraZenica) (Keyhanian et al., 2020). We have the following comments and concerns.

A mechanism responsible for neuro-COVID not considered by the authors is the damage of the CNS/PNS by the empiric treatment applied to COVID-patients. Most of the COVID-19 patients receive antivirals, antibiotics, chloroquine, steroids, and biologicals (e.g. tocilizumab (IL-6 blocker). From remdesivir, ritonavir, and lopinavir it is known that they occasionally trigger rhabdomyolysis (Ghasemiyeh et al., 2020). From chloroquine it is well known that it may cause toxic myopathy (Carvalho, 2020). Known side effects of tocilizumab include arterial hypertension, hyperlipidemia, obesity, infections, bowel ulceration, and heart failure (Saito et al., 2020), which may secondarily cause cerebrovascular disease. From azithromycin and meropenem, and linezolid it is well known that they are myotoxic. In a single COVID-19 patient chloroquine triggered the development of a myasthenic syndrome (Koc et al., 2020).

A second mechanism responsible for neuro-COVID not considered by the authors is secondary CNS/PNS damage through affection of other organs by the virus. These other organs particularly include the heart and the arteries. Ischemic stroke in COVID-19 may not only result from thrombus formation due to hyper-coagulability directly in the brain but also from thrombus formation in distant veins from where thrombi may embolise via a patent foramen (PFO) to the CNS. There is also evidence that SARS-CoV-2 may cause myocarditis (Othenin-Girard et al., 2020) which may lead to intra-ventricular thrombus formation and secondarily to ischemic stroke. Myocarditis may also go along with heart failure, which may lead to low output failure and consecutively cerebral watershed infarctions. Myocarditis may be also complicated by supra- or ventricular arrhythmias, which may secondarily lead to intra-ventricular thrombus formation and eventually ischemic stroke. Severe COVID-19 may be complicated by arterial hypertension, which may eventually cause ischemic stroke or intra-cerebral bleeding (ICB). Arterial hypertension may also result from affection of the kidneys by the viral infection, which may be complicated by renal hypertension and secondarily by stroke or ICB.

The authors propose hypoxic injury as a possible mechanism underlying CNS/PNS involvement in COVID-19 (Keyhanian et al., 2020). Cerebral hypoxia usually results from near drowning, asphyxia, cardiac arrest, or respiratory failure. Whether cerebral hypoxia may result from extra-corporal membrane oxygenation (ECMO) therapy, frequently required for COVID-19 patients with severe acute respiratory distress syndrome (ARDS), remains unproven. Supposing that global CNS hypoxia is responsible for neuro-COVID, typical features on cerebral imaging should be present. First, primarily the grey matter, such as the cortex, basal ganglia (BG), thalami, the cerebellum, and hypocampi should be affected. Second, lesions at these locations should show up as diffuse edema, loss of grey/white matter differentiation, BG hypodensity, reversal sign, white cerebellum sign, linear hyperdensity outlining the cortex, and pseudo-subarachnoid bleeding on cerebral computed tomography (CCT), and as cytotoxic edema on multimodal magnetic resonance imaging (MRI) within the first 24 h after hypoxia (Bell and Di Muzio, 2020). MRI lesions are hyperintens on T2-imaging. These lesions are followed by pseudo-normalisation after about 1 week (Bell and Di Muzio, 2020). After 1–2 weeks T1-hyperintensity indicating cortical laminar necrosis becomes evident (Bell and Di Muzio, 2020). However, such dynamic lesions have not been described in patients with neuro-COVID, why it is unlikely that cerebral hypoxia plays a crucial role in the development of neuro-COVID. Additionally, most patients with COVID-19 develop respiratory failure subacutely, why most of them are intubated and ventilated in due time and thus not become hypoxic.

Neurological manifestations of COVID-19 not addressed in the review were movement disorders (e.g. myoclonic ataxia syndrome) (Cunha et al., 2020), cerebellitis (Fadakar et al., 2020), acute necrotising encephalitis (Ghosh et al., 2020), limbic encephalitis (Guilmot et al., 2020), cerebral vasculitis (Vaschetto et al., 2020), pituitary apoplexia

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(Solorio-Pineda et al., 2020), posterior reversible encephalopathy syndrome (PRES) (Anand et al., 2020), and dermatomyositis (Gokhale et al., 2020).

Overall, the valuable review by Kayhanian et al. has some limitations which should be met before the conclusions drawn can be justified. Mechanisms leading to neuro-COVID may be more variable than anticipated. Treatment may occasionally be more harmful than beneficial.

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JF: design, literature search, discussion, first draft, critical comments.

Informed consent

Was obtained.

Declaration of Competing Interest

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