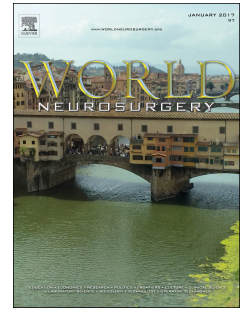


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Mechanisms of neurological injury in COVID -19

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Title page

Type of article: Letter to Editor

Title: Mechanisms of neurological injury in COVID -19

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Title: Mechanisms of neurological injury in COVID -19.

We read with much interest the article “Neurological Impact of Coronavirus Disease (COVID-19): Practical Considerations for the Neuroscience Community” by Werner et al. published in your esteemed Journal. Authors have described the various neurological details of COVID - 19 in detail.¹ We believe this topic is important and is continuously evolving. We have the following comments as an addition to the article.

Symptomatic patients with COVID -19 can present with mild, moderate, or severe illness.

Across all studies, patients with severe illness have multi-organ involvement. Patients with severe disease are prone to develop acute respiratory distress syndrome (ARDS), acute cardiac injury, acute renal failure, acute liver dysfunction.² While several patterns of central nervous system involvement have been reported among these patients, diffuse CNS involvement has been reported to be higher.³

Multiple mechanisms could contribute to the initiation and progression of CNS injury in COVID - 19 patients.

i] Cytokine storm, defined as dysfunctional, uncontrolled, continuous activation of inflammation has been consistently reported across all studies. This exaggerated inflammation has been postulated to contribute to ARDS, myocardial injury, renal failure, severity of illness, requirement of intensive care unit admission, requirement of mechanical ventilation, and mortality. This has been diagnosed with an elevated level of inflammatory markers including C-reactive protein, leukocytes, pro calcitonin, proBNP, ferritin, interleukins, and various other

inflammatory markers. While diffuse CNS involvement is noted to be higher among patients with severe illness, a temporal association between inflammatory markers and CNS dysfunction is not yet shown.^{4,5}

ii] Autopsy studies on COVID -19 patients have been limited. Direct viral invasion has been reported in various organs including lung, liver, and heart. However, no reports have yet identified the virus, or viral particles in the brain.⁶

iii] hypoxia induced apoptosis and ischemia, presenting in most patients as multiorgan dysfunction.⁷

iv] prothrombotic state secondary to endothelial injury, thrombocytopenia, deranged coagulation parameters as evident from the raised D-dimer, fibrinogen, prothrombin time.^{6,8}

v] embolic events secondary to myocardial dysfunction, with increased risk of arrhythmia. This has been supported by the presence of several raised cardiac markers including high-sensitivity troponins, and D-dimer.^{6,8,9}

vi] among patients with severe illness multiple other contributors of central nervous system dysfunction requiring consideration are a) prolonged requirement of CNS depressing agents including benzodiazepines [Diazepam, Midazolam], Opioids [Fentanyl, Morphine], anesthetic agent [propofol], and neuromuscular blocking agents to achieve better ventilation goal in patients with severe ARDS, b) prolonged ICU stay, c) presence of cardiogenic and septic shock, d) CNS side effects of other medications including corticosteroid, antibiotics etc.^{6,9-11}

Finally, cerebrovascular injury is being commonly reported in patients with COVID-19. Studies have shown that patients with severe COVID-19 had higher cardio-cerebrovascular comorbidities including older age, hypertension, diabetes mellitus, hyperlipidemia, heart failure, coronary artery disease, and cerebrovascular disease.^{12,13} A recent study also showed that patients with severe COVID-19 had higher cerebrovascular events as compared to patients without severe illness.³ We agree with the authors that future studies will be instrumental in clarifying patterns, predictors and outcome of COVID-19 related neurological injury,

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