Pathophysiology of Neuro-COVID

Abstract: With interest we read the review article by Battaglini et al., 2020 about the pathophysiology of neurological disease in SARS-CoV-2 infected patients with COVID-19. The authors discuss three possible mechanisms, viral neurotropism, hypercoagulopathy, and inflammation, and brain-lung crosstalk. We have the following comments and concerns.

Keywords: brain, peripheral nerves, COVID-19, SARS-CoV-2, pathophysiology.

Letter to the Editor

With interest we read the review article by Battaglini et al., 2020 about the pathophysiology of neurological disease in SARS-CoV-2 infected patients with COVID-19 (Battaglini, D. et al., 2020). The authors discuss three possible mechanisms, viral neurotropism, hypercoagulopathy, and brain-lung crosstalk (Battaglini, D. et al., 2020). We have the following comments and concerns.

Neurological disease in SARS-CoV-2 infected patients may not only be due to direct viral attack, the inflammatory response, hypercoagulopathy, or brain-lung interactions but also due to other mechanisms. These include side effects of drugs given for SARS-CoV-2, hypoxia due to affection of the lungs, heart, or kidneys or side effects of long-term treatment of COVID-19 patients on the ICU. It is well established that drugs such as steroids, chloroquine, protease-inhibitors (lopinavir/ritonavir), remdesivir, azithromycin, tocilizumab, and cromstat are potentially accompanied by severe neurological side effects. Steroids may cause mitochondrial myopathy. From protease-inhibitors it is known that they carry a potential to trigger sensory neuropathy (Ellis, R. J. et al., 2008). Azithromycin carries the risk of triggering rhabdomyolysis (Teng, C. et al., 2019). Adverse events attributed to tocilizumab were facial palsy and diplopia (Dastan, F. et al., 2020).

Concerning neurotropism, there is little evidence that SARS-CoV-2 causes meningitis, encephalitis, ventriculitis, or myelitis by a direct attack of the virus against neurons, glial cells, or endothelial cells. Only few cases with infections CNS disease and confirmation of the virus in the cerebro-spinal fluid (CSF) or brain tissue have been reported (Etemadifar, M. et al., 2020). In the majority of the cases with meningitis / encephalitis / ventriculitis / myelitis in COVID-19 patients, the infectious agent is either another neurotropic virus or neurological disease is immune-mediated, manifesting as auto-immune encephalitis (AIE), acute, hemorrhagic, necrotising encephalopathy (AHNE), acute disseminated encephalomyelitis (ADEM) (Finsterer, J., & Scorza, F. 2020), or myelitis (Durrani, M. et al., 2020). Concerning hypercoagulability, the number of patients with ischemic stroke due to forced thrombus formation is low compared to the huge number of SARS-CoV-2 infected patients (>30Mill as of 15th September 2020). If hypercoagulability is truly a pathophysiological factor one would expect a significant increase in the stroke-rates since the outbreak of the pandemic, which is actually not the case. By the way, pathomechanism three should be rather termed as “lung-brain crosstalk” than as “brain-lung crosstalk”.

The most likely pathophysiological mechanism of CNS/PNS disease associated with COVID-19 is the immunological reaction to the virus. Arguments for immune-mediated neurological disease in COVID-19 patients is that...
immune-suppressive treatment for neurological complications can be highly effective, that the virus is usually undetectable in the CSF or CNS tissue, and that CNS/PNS disease in COVID-19 patients frequently resembles immune-mediated CNS/PNS disease due to other causes. Examples of immune-mediated PNS disease in COVID-19 patients include Guillain-Barre syndrome (GBS) and myasthenia gravis (MG) (Finsterer, J. et al., 2020; Restivo, D. A. et al., 2020; & Restivo, D. A. et al., 2020). In a recent mini-review COVID-19-associated GBS has been reported in 62 patients (as of 12th August) [8fi]. Among these 62 patients age ranged from 11 to 94 years. In 56 patients sex was reported and 20 patients were female and 36 were male. Onset of GBS was after onset of COVID-19 in 58 patients. Time between onset of COVID-19 and GBS ranged between 3 and 33 days. Acute inflammatory demyelinating neuropathy (AIDP) was diagnosed in 42 patients, acute motor and axonal neuropathy (AMAN) in 6 patients, Miller-Fisher syndrome (MFS) in 5 patients, and acute, motor, sensory, axonal neuropathy (AMSAN) in 3 patients. In 6 patients the subtype was not specified. The virus was not detected in the CSF in any of the 62 patients. Treatment included steroids (n=2 patients), intravenous immunoglobulins (IVIG) (n=50 patients), plasmapheresis (n=8 patients), or artificial ventilation (n=18 patients). Twenty-four patients recovered completely and 23 partially. Two patients died. Concerning MG, recently, three patients have been reported in whom SARS-CoV-2 triggered the development of MG [8Restivo]. Additionally, in a mini-review exacerbation of MG occurred in half of the 16 investigated MG patients (Finsterer, J. et al., 2020).

Overall, the review has a number of shortcomings. All neurological conditions associated with COVID-19 should be addressed. The various pathomechanisms of neurological disease in SARS-CoV-2 infected patients need to be delineated to develop specific treatment for each of the neurological COVID-19 manifestations.

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**REFERENCES**


