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.

Brain, Behavior, and Immunity 88 (2020) 35

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Letter to the Editor

Do matrix metalloproteases mediate the SARS-CoV-2-related damage to the central nervous system?

Dear Editor,

We have read with great interest the article "Nervous system involvement after infection with COVID-19 and other coronaviruses" by Wu at al. The Authors are to be commended for their timely review of the possible mechanisms of damage to the nervous system by coronaviruses.

More specifically, the Authors outlined four potential mechanism of injury, the first being related to a direct infection via either a hematogenous or neuronal pathway. In this regard, we would like to highlight the fact that many pathological mechanisms reported by the Authors have been linked to the effects of Matrix metalloproteases (MMPs), enzymes that participate in remodeling the extracellular matrix (ECM). Even more interestingly, a significant MMP overexpression has already been reported in a murine model of encephalitis caused by a coronavirus (Zhou et al., 2005).

For instance, concerning the "blood circulation pathway", the Authors described the relevant role of Blood-brain barrier dysregulation (BBB). In this regard, Rempe et al. recently reviewed the fundamental contribution of MMP upregulation to BBB malfunction, with implications not only on infectious diseases but also on both stroke, epilepsy, Alzheimer's and Parkinson's diseases. (Rempe et al., 2016) Furthermore, the Authors also described the mechanism of local release of interleukines, just as other studies in literature have already established the role played by MMPs in mediating bacterial invasion, neutrophil infiltration as well as the cytokine signaling in neuroinfectious diseases (Muri et al., 2019).

When dealing instead with the "neuronal pathway", Wu et al. described a demyelination mechanism. In this regard, MMPs have been shown to digest myelin basic protein, thus causing demyelination both in animal models and human tissue (Muri et al., 2019). Moreover, the recent rise in the incidence of Kawasaki disease may further support the conjecture of a SARS-CoV-2 tissue damage mediated by MMPs (Verdoni et al., 2020). As a matter of fact, Kawasaki disease has already been linked to coronavirus infections and is strongly related to a viral induced epigenetic overexpression of MMP-9 (Kuo et al., 2017).

Since MMPs can have multiple effects on the ECM of different tissues, it is of relevance that their upregulation may not exhaust its effect in the acute setting. This raises the question of the potential long-term MMPs-mediated effects of SARS-CoV-2 infection on CNS tissues. For instance, it is already well known that MMPs (and in particular MMP-9) contribute to both formation, growth, and rupture of cerebral aneurysms by digesting the ECM, which leads to ballooning of blood vessels (Rempe et al., 2016).

Hence, continuous monitoring for potential mid- and long- term pathological effects on the CNS related to the SARS-CoV-2 infection is advised.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.05.050.

References

Kuo, H.C., Li, S.C., Huang, L.H., Huang, Y.H., 2017. Epigenetic hypomethylation and upregulation of matrix metalloproteinase 9 in Kawasaki disease. Oncotarget 8 (37), 60875–60891. https://doi.org/10.18632/oncotarget.19650. eCollection 2017 Sep 22.

Muri, L., Leppert, D., Grandgirard, D., Leib, S.L., 2019 Aug. MMPs and ADAMs in neurological infectious diseases and multiple sclerosis. Cell Mol. Life Sci. 76 (16), 3097–3116. https://doi.org/10.1007/s00018-019-03174-6. Epub 2019 Jun 6.

Rempe, R.G., Hartz, A.M.S., Bauer, B., 2016. Matrix metalloproteinases in the brain and blood-brain barrier: Versatile breakers and makers. J. Cereb. Blood Flow Metab. 36 (9), 1481–1507. https://doi.org/10.1177/0271678X16655551. Epub 2016 Jun 20. Review.

Verdoni, L., Mazza, A., Gervasoni, A., Martelli, L., Ruggeri, M., Ciuffreda, M., Bonanomi, E., D'Antiga, L., 2020. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet https://doi.org/10.1016/ S0140-6736(20)31103-X.

Zhou, J., Marten, N.W., Bergmann, C.C., Macklin, W.B., Hinton, D.R., Stohlman, S.A., 2005 Apr. Expression of matrix metalloproteinases and their tissue inhibitor during viral encephalitis. J. Virol. 79 (8), 4764–4773.

Daniele Bongetta[a,*], Tommaso Calloni[b], Elena Virginia Colombo[a], Alessandro Versace[a], Roberto Assietti[a]

[a] *Neurosurgery Unit, ASST Fatebenefratelli-Sacco, Ospedale Fatebenefratelli e Oftalmico, Milano, Italy*

[b] *Unit of Neurosurgery, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy*

E-mail address: danielebongetta@hotmail.com (D. Bongetta).

[*] Corresponding author at: SC Neurochirurgia, Ospedale Fatebenefratelli e Oftalmico, Piazzale Principessa Clotilde 3, 20121 Milano, Italy.

https://doi.org/10.1016/j.bbi.2020.05.050
Received 18 May 2020; Accepted 18 May 2020
Available online 21 May 2020
0889-1591/