Journal of Neuroradiology xxx (2020) xxx–xxx

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Potential underlying mechanisms of cerebral venous thrombosis associated with COVID-19

With interest, we read the paper of Poillon et al. about the possible association between the development of cerebral venous thrombosis and coronavirus disease-2019 (COVID-19) [1]. Although the authors mentioned that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause hyperactivation of inflammatory factors and damage to the coagulation system, increasing the risk of deep vein thrombosis, cerebral venous thrombosis and pulmonary embolism, the underlying pathogenesis was not discussed in detail. For this reason, we want to highlight in the present manuscript the potential underlying pathophysiological mechanisms of these virus infection-related thromboembolic events.

A substantial proportion (5–15%) of patients with severe COVID-19 develop venous and arterial thromboembolic complications [2]. As an example, several recent papers have reported a cerebral venous thrombosis as an initial presentation of COVID-19 [1,3,4]. These phenomena are probably related to a combination of low-grade disseminated intravascular coagulation (DIC) and a localised pulmonary thrombotic microangiopathy. The COVID-19 coagulopathy is characterised by an increased amount of D-dimers, a high fibrinogen, a mildly prolonged prothrombin time, and a modest thrombocytopenia. Although this picture could be suggestive for a DIC, the diagnosis of DIC, according to the DIC score of the International Society on Thrombosis and Haemostasis, is often not retained in patients with a SARS-CoV-2 infection as the level of D-dimers is remarkably higher and the consumption of platelets is lower than in e.g. sepsis-induced coagulopathy. Besides, increased concentrations of lactate dehydrogenase and ferritin are often measured, as seen in patients with thrombotic microangiopathy. The hypercoagulable state in COVID-19 is illustrated by post-mortem findings, e.g. microvascular platelet-rich thrombotic depositions in the small vessels of the lungs. However, signs of hemolysis or schistocytes in the blood film are absent and a higher platelet count is measured in comparison to thrombotic microangiopathy [5]. Antiphospholipid antibodies can arise transiently and may also play a yet unresolved role in the pathophysiology of thrombosis associated with COVID-19 [6].

Looking at the underlying mechanisms for developing thrombosis, the three criteria of Virchow's triad (stasis, endothelial injury or vessel wall injury, and hypercoagulability) are fulfilled in critically ill COVID-19 patients. More specifically, immobility and prone position result in reduced venous flow [6]. Hypoxia leads to vasoconstriction and reduced blood flow, contributing to endothelial dysfunction. Besides, the basal anti-inflammatory and antithrombotic phenotype of the endothelium can be changed into a proinflammatory and procoagulant phenotype by the alteration of transcriptional factors [e.g. hypoxia-inducible factor 1 (HIF-1) and early growth response gene 1 (Egr1)] as previously reported in other acute respiratory distress syndromes (ARDS) [2]. In severely COVID-19 cases, a "cytokine storm" with high concentrations of proinflammatory cytokines and chemokines [tumour necrosis factor-α (TNF-α) and interleukins (IL), including IL-1β and IL-6] suppress anticoagulant pathways, release ultralarge von Willebrand factor multimers and can induce tissue factor (TF) expression. Neutrophils, monocytes, platelets and microparticles in the circulation bind to the activated endothelium and local provide TF and neutrophils extracellular traps (NETs) for initiation of coagulation via the TF/FVIIa pathway. This results in the generation of excessive amounts of thrombin with a subsequent formation of e.g. pulmonary microthrombotic vaso-occlusions. The hypercoagulable state is further achieved by an imbalance between increased procoagulant factors (e.g. fibrinogen, FV, and FVIII) and potentially decreased or normal natural coagulation inhibitors (e.g. proteins C and S, and antithrombin) [2,7].

Disclosure of interest

The authors declare that they have no competing interest.

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https://doi.org/10.1016/j.neurad.2020.06.009

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Please cite this article in press as: Speeckaert MM, et al, Potential underlying mechanisms of cerebral venous thrombosis associated with COVID-19, J Neuroradiol (2020), https://doi.org/10.1016/j.neurad.2020.06.009