

Figure 1. Integrative concepts of the pathophysiology of COVID-19-related central nervous system complications. This figure integrates the clinical and experimental data linking maladaptive innate immunity-related systemic hyperinflammation (provoked by the binding of SARS-CoV-2 S1 to ACE2-expressing cells in the lung and intestine) to neurovascular endothelial dysfunction, BBB breakdown and CNS innate immune activation, potentially contributing to SARS-CoV-2-related CNS complications. It demonstrates subsequent endothelial injury in the peripheral vasculature due to direct viral endothelial infection causing endotheliits and potential endothelial ACE2 downregulation; similar mechanisms may also involve the neurovascular unit. It also depicts the proposed role of infiltrating protective immune cells, migrating from the bloodstream into the CNS parenchyma through the disrupted BBB, in limiting CNS injury and promoting viral clearance.²⁵

ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; Ang II, angiotensin II; AT, angiotensin; BBB, blood-brain barrier; CCL, CC chemokine ligand; CNS, central nervous system; CXCL, chemokine (C-X-C motif) ligand; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; MAP, microglial activation and proliferation; MMPs, matrix metalloproteinases; NK, natural killer; PRRs, pattern recognition receptors; SARS-CoV-2 S1, severe acute respiratory syndrome coronavirus 2 spike glycoprotein 1; TNFα, tumour necrosis factor-α

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