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.

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Brief Commentary

The next chapter for COVID-19: A respiratory virus inflames the brain

William A. Banks [a,b,*], Michelle A. Erickson [a,b]

[a] Geriatric Research Education and Clinical Center, Veterans Affairs Puget Sound Health Care Center, Seattle, WA, USA
[b] Gerontology and Geriatric Medicine, Department of Medicine, School of Medicine, University of Washington, Seattle, WA, USA

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the new century's most severe pandemic. COVID-19, the respiratory disease caused by SARS-CoV-2 infection, can be mild or devastating and in all too many cases, it is deadly. Neurological symptoms are also common, affecting as many as 1/3 of COVID-19 patients, and include headache, fatigue, myalgia, impaired taste and smell, cognitive impairment, and delirium as well as other less common manifestations (Misra et al., 2021). What is less clear is how a respiratory virus such as SARS-CoV-2 can contribute to these neurological symptoms. The recent publication by Frank et al entitled "SARS-CoV-2 spike subunit induces neuroinflammatory, microglial and behavioral sickness responses: evidence of PAMP-like properties" gives many insights into the manifestations of COVID-19 as a Brain Disease (Frank et al., in press).

Frank et al concentrated on S1, an approximately 120 kDa glycoprotein that is part of the spike protein (S protein), SARS-CoV-2′s viral attachment protein (VAP). VAPs determine which cells a virus can invade and how efficiently they are taken up. The SARS-CoV-2 variants all involve mutations in the S protein, explaining their varying degrees of infectivity, and it is S protein that induces the immune reaction of the mRNA vaccines. Viral proteins can be very toxic as illustrated by HIV-1′s Tat protein and its VAP, gp120. Thus, as Frank et al astutely realized, study of S1 in the absence of productive infection can reveal much about how SARS-CoV-2 induces neuroinflammation and brain disease.

Even in the absence of productive infection, immune-active S1 that is first produced systemically has many routes by which it can affect the brain. Induction of the cytokine storm could disrupt the blood–brain barrier (BBB), alter BBB transporters, increase immune cell trafficking into brain, alter the blood concentration of transporter substrates, provide higher blood levels of those cytokines that are transported across the BBB, and induce brain endothelial cells to secrete neuroimmune substances directly into the brain (Erickson et al., 2018; Erickson et al., 2021). S1 circulating free in blood can cross the BBB (Rhea et al., 2021), and it seems likely that SARS-CoV-2 can also enter the brain by crossing the BBB and other mechanisms. Therefore, S1 that is shed from SARS-CoV-2 in the brain or periphery may be a source of S1 in the CNS.

S1 in the brain is likely to be much more neuroinflammatory than S1 in the blood. Frank et al show S1 injected directly into the brain can induce some sickness behaviors, increase brain levels of cytokines, and activate microglia and astrocytes. Notably, the S1-induced symptomatology described by Frank et al is also not classic sickness behavior as weight loss/anorexia were not among its features. Most of the parameters that were characterized by Frank et al. were measured in the acute (24 h post) or subacute (7 days post) phases after S1 injection. It is noteworthy, then, that Frank et al found that 7 days after central administration of S1, neuroinflammation persisted, although the pattern had changed. The only cytokine still elevated on day 7 was TNF. Intriguingly, the patterns of neuroinflammation differed among brain regions at day 7. For example, *GFAP* was only elevated in hippocampus and *TLR2* was only elevated in hypothalamus. *Cd200r1* was elevated in hippocampus and hypothalamus at 24 h, but was decreased below controls levels at day 7 in hippocampus and frontal cortex. These findings raise the possibility that the variability in the neurological symptoms of COVID-19, both temporally and among patients, has a basis in these shifting patterns of neuroinflammation. Clearly, more work needs to be done parsing the patterns of S1-induced inflammation and correlating those patterns to symptomatology.

Among many of the survivors of COVID-19 looms a second chapter in their illness: Long Covid. Characterized by many symptoms indicative of CNS involvement, Long Covid strikes over 50% of non-hospitalized COVID-19 patients (Blomberg et al., 2021) with fatigue, brain fog, and other symptoms lingering with little improvement for months (Blomberg et al., 2021; Davis et al., 2021)

Most patients (75–90%) with Long Covid had milder cases of COVID-19 not requiring hospitalization (Davis et al., 2021; Vanichkachorn et al., 2021), and so the symptomatology cannot be simply ascribed to a post-intubation syndrome or having survived a near death experience. Some fear that Long COVID may evolve into a chronic neurodegenerative syndrome characterized by cognitive impairment (Hascup and Hascup, 2020; Meier et al., 2021). A characteristic of Long Covid is its persistence, with little resolution of symptoms 7 months post-infection (Davis et al., 2021). Although some symptoms do improve (e.g., fever, cough, shortness of breath), others do not (fatigue, palpitations, muscle

* Corresponding author at: VAPSHCS, 1660 S Columbian Way, Seattle, WA 98108, USA.

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aches, bone aches) and some became more severe (post-exertional malaise, brain fog, memory, speech and language issues). Studies like those of Frank et al. which evaluate not only the onset but persistence of symptoms and biochemical parameters in models of SARS-CoV-2-associated CNS dysfunction are needed to provide more insight on Long Covid mechanisms.

ACE2, a membrane bound enzyme, has been hailed as the protein to which S1 binds and so accounts for the infectivity of SARS-CoV-2. However, VAPs bind to their ligands in a stochastic fashion and do not follow classic receptor-ligand binding kinetics. As such, many viruses co-opt a variety of cell surface glycoproteins and glycolipids to serve as anchors and "receptors" (Schweighardt and Atwood, 2001). Evidence suggests that S1 binds to sites other than ACE2 and ACE2 seems to play little or no role in the uptake of S1 by the BBB, liver, kidney, or spleen (Rhea et al., 2021). Frank et al found that S1 activated microglia in vitro, yet microglia did not express ACE2. Therefore, Frank et al investigated other possible receptors and found involvement of TLR2 and TLR4. An over-emphasis of the role of ACE2 is, therefore, likely to miss much of what S1 and its virus can do and therapeutics targeted solely at ACE2 are unlikely to be totally effective.

In summary, S1 induces inflammation and once in the brain can directly induce neuroinflammation. Its abilities to cross the BBB and to activate microglia and likely other cells comprising the neurovascular unit strongly suggest that it may be a major cause of CNS-related symptomatology of COVID-19. Once induced, neuroinflammation is persistent and so may underly the symptomatology of Long Covid. Clearly, more work needs to be done investigating how S1 and SARS-CoV-2 affect brain, behavior, and immunity.

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