Update on the Pathogenesis and Treatment of Long COVID Syndrome

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Commentary

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ABOUT THE STUDY

The persistence of vascular and thrombotic complications has been identified as a significant contributing factor in Long COVID Syndrome (LCS). Previously, we hypothesized that this thrombotic vasculopathy is triggered by the continuous expression of the Spike protein, whether due to natural viral infection or ModRNA COVID "vaccines," in various tissues and organs. Furthermore, we postulated that the persistent expression of the Spike protein induces a hyperactive immunoinflammatory response [1]. This phenomenon has been termed Long COVID Syndrome due to Natural Viral Infection (NSITV) or ModRNA Vaccines (VSITV), primarily attributed to Spike protein-induced thrombotic vasculopathy linked to a hyperactive immunoinflammatory response.

Three recent studies provide substantial and irrefutable evidence supporting this hypothesis.

The first study, conducted by Etheresia Pretorius et al. [2], used Fibrin Amyloid Microclots (FAM) and Neutrophil Extracellular Traps (NETs) as markers of thromboinflammation. Pretorius and collaborators discovered that NET markers are quantitatively and structurally associated with the size and amount of FAM in LCS patients. These markers demonstrated strong diagnostic performance, both independently and in combination. The study suggests that NETs may be components of circulating FAM, and increased NET formation may stabilize FAM in the circulation, leading to detrimental effects that causally contribute to LCS.

The second study by Dalton et al. [3] found that, as a cohort, the platelet-poor plasma from long COVID samples exhibited higher microclot counts compared to control groups, although the counts varied widely. Similarly to Pretorius et al., Dalton and colleagues concluded that FAM and NETs could serve as biomarkers for the disease and as potential treatment targets for LCS patients.

The third study by Ryu, et al. [4], considering that fibrinogen, the central structural component of blood clots, is abundantly deposited in the lungs and brains of COVID-19 patients, correlates with disease severity, and is a predictive biomarker for post-COVID-19 cognitive deficits; Ryu and collaborators demonstrated that fibrin binds to the Spike protein of SARS-CoV-2, forming pro-inflammatory blood clots that drive systemic thromboinflammation and neuropathology in COVID-19. Fibrin, acting through its inflammatory domain, is necessary for oxidative stress and macrophage activation in the lungs, while suppressing natural killer cells, following SARS-CoV-2 infection. Thus, the study shows that the interaction of the Spike protein, whether of natural (viral infection) or recombinant origin (ModRNA), with fibrin promotes neuroinflammation and neuronal loss, as well as innate immune activation in various tissues and organs.

Regarding treatment, a reasonable approach has been proposed for severe LCS, considering the role of thrombotic vasculitis linked to hyperimmune-inflammatory responses. It includes a combination of anti-inflammatory steroids

(deflazacort 15-30 mg/day, prednisolone 10-20 mg/day), anticoagulants (apixaban 5-10 mg/day, dabigatran 110-150 mg/day), antiplatelet agents (clopidogrel 75 mg BID, ticagrelor 60-90 mg/day), and rapamycin 1 mg BID or everolimus 10 mg/day or Janus Kinase inhibitors (Tofacitinib 5-10 mg BID, Baricitinib 4mg/day). In cases of mild to moderate LCS, lower doses of corticosteroids, anticoagulants, and antiplatelet agents should be considered. If no improvement is observed, rapamycin or a Janus Kinase inhibitor can be added. The use of monoclonal antibodies targeting the inflammatory domain of fibrin to block its interaction with the Spike protein could be considered to protect against microglia activation and neuronal injury, as well as against thromboinflammation in affected tissues and organs. Prospective clinical trials are needed to formally test this proposed treatment.

What is needed now?

It is crucial to develop techniques to detect spike protein expression in various tissues and organs and to find ways to eliminate these proteins from the body.

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