Review 1: "SARS-CoV-2 Spike Protein Accumulation in the Skull-Meninges-Brain Axis: Potential Implications for Long-Term Neurological Complications in post-COVID-1"

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The MIT Press

Published on: May 18, 2023

URL: https://rrid.mitpress.mit.edu/pub/objrfvv1

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**RR:C19 Evidence Scale** rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

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**Review:**

Dr. Rong and colleagues clearly describe their findings of S1 and N proteins and RNAs in human post-mortem skull, meninges and brain tissues of COVID-19 patients and uninfected controls, inflammatory and coagulation factors associated with S1 deposit, and similar pathology in mouse tissues after injection of S1 protein.

1) These data definitively link COVID-19 pathology to the acute and sustained presence of S1 protein.

2) These data also definitively show involvement of immune/inflammatory/coagulation mediators in the S1-evoked CNS pathogenesis of COVID-19. The co-localization of SARS-CoV-2 proteins and immune/inflammatory/coagulation mediators in human brain tissue is the most important new finding of this study.

3) Although the data suggest a possible transmission of SARS-CoV-2 RNAs and proteins from skull marrow to CNS parenchyma, the actual occurrence of such transfers and any role they have in COVID-19 are only weakly supported. Finding S1 protein in two locations does not prove effective transmission from one to the other site. If the mouse model could be used to quantitatively assess transfer of labeled S1 protein from skull marrow to brain parenchyma, blood to brain parenchyma and CSF to brain parenchyma in parallel, this would be better proof of an actual axis that meaningfully participates in movement of S1 protein in COVID-19 infection.

4) Demonstration of multi-organ system involvement in mice injected with S1 protein has little value in this report. There are already many descriptions of such multi-organ system distribution of SARS-CoV-2 proteins in COVID-19 infection in the literature. Unless a new dimension is explored - such as detailed kinetics of distribution - or the model is used to directly and quantitatively assess a skull marrow-brain parenchyma axis, then the findings described don't add to any understanding of COVID-19 pathogenesis.

5) All human findings are in post-mortem tissues, although others have demonstrated S1 and N RNAs and proteins in living humans. These reports are not cited in references.