Rapid Reviews COVID-19

Review 2: "SARS-CoV-2 invades cognitive centers of the brain and induces Alzheimer's-like neuropathology"

Neville Vassallo¹

¹"Associate Professor University of Malta Faculty of Medicine and Surgery Department of Physiology and Biochemistry MALTA"

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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.

Review:

Shen et al. present a very interesting work that attempts to link SARS-CoV-2 infection of the brain with an "Alzheimer's-like" pathology. The study is based on brains and iPSC-derived neurons from five COVID-19 patients (2 autism cases, 1 AD case, 1 FTD case, and 1 healthy case). Broadly speaking, the authors need to demonstrate two important aspects: (1) the presence of SARS-CoV-2 virus in brain cortical areas and its ability to directly infect neurons; and (2) provide evidence that SARS-CoV-2 can induce the primary pathological features of Alzheimer's disease (AD): amyloid deposition (A β), neurofibrillary tangle formation (p-Tau) and neuronal loss.

Regarding (1), the neurotropism of SARS-CoV-2 is convincingly demonstrated, and this is consistent with other reports. Spike and nucleocapsid proteins and viral RNA are detected in neuronal cytoplasm and neuritic processes in three cortical regions, SARS-CoV-2 infects mature cortical neurons, and infectivity correlates with expression of the ACE2 receptor as a key route of entry. Regarding (2), immunohistochemical staining shows highly significant increases in COVID-infected cases of A β and p-Tau deposits in cortical regions and hippocampus. In one figure inset, we see Thioflavin T-staining of cellular A β aggregates, which is an important defining characteristic of A β deposits in AD; it would have been nice to see more examples of this (with quantification of fibrillar ThT-positive aggregates and perhaps even isolation and confirmation of fibrils by AFM).

Data showing significantly higher neuronal apoptosis by caspase-3 activation in the COVID-19 cases are also presented. Evidence of a neuroinflammatory response in the SARS-CoV-2 infected brains is also provided by IL-1 and IL-6 positivity. Most of the evidence presented thus far is derived from immunohistochemical staining and analysis of brain sections. To establish a more direct link between SARS-CoV-2

infection and an Alzheimer's phenotype, virus-infected iPSC-derived differentiated neurons from healthy and AD individuals exhibited significantly increased cellular A β and p-Tau aggregates, together with enhanced expression of AD-related genes like BACE1 (but not APP, PS1/2), and activated caspase-3. Notably, the AD-derived neurons were more affected by these changes than the healthy-derived ones. Finally, the authors claim an "AD signature" for 24 genes upregulated in common in differentiated neurons infected by SARS-CoV-2 and AD patients.

To conclude, the collective experimental results presented in this paper do reliably substantiate the hypothesis that SARS-CoV-2 infects cortical neurons of the brains of COVID-19 patients and triggers, or exacerbates, certain pathological features reminiscent of an Alzheimer-like pathology. However, although compelling, the 'specificity' of the induction is still not unequivocal. Only a 4% gene overlap was observed between the AD group and the SARS-CoV-2 infected group, and, importantly, overexpression of the top 3 of these genes failed to trigger cellular A β or p-Tau aggregation. The mechanisms have to be probed further, for instance by *in vivo* animal studies, and the findings replicated in larger numbers for more certainty regarding these claims. Nonetheless, considering these limitations, the study represents a formidable hypothesis that can have very important implications considering the millions of people infected around the world with SARS-CoV-2, not only during acute infection but also in the longer term.