Rapid Reviews COVID-19

Review 1: "SARS-CoV-2 invades cognitive centers of the brain and induces Alzheimer's-like neuropathology"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

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Review:

Shen and colleagues have reported brain pathological findings of five COVID-19 patients with or without pre-existing neurological disorders, such as Alzheimer's dementia or autism. First, the authors have supported SARS-CoV-2 neurotropism, showing the direct viral invasion of cerebral hubs involved in cognitive functions by means of ACE2 and neuropilin-1-dependent mechanisms typical of mature neurons. Second, SARS-CoV-2 infection has been found to be able to trigger or enhance β-amyloid pathology underlying Alzheimer's neurodegeneration as well as to increase neuroinflammation and induce several cell death pathways, such as apoptosis. Third, the authors replicated SARS-CoV-2-induced neurodegenerative changes by silencing the top three downregulated genes in human neurons.

The study is very interesting, well-written, and potentially informative since it could pave the way towards putative mechanisms underlying neuropathology associated with SARS-CoV-2 infection. However, the small number of examined brains and the impossible evaluation of within-patient changes induced by SARS-CoV-2 infection (i.e. assessing brain samples before COVID-19) are major limitations that prevent a strong generalization of the authors' results. For example, a higher number of extracellular β-amyloid plaques in Alzheimer's patients with COVID-19 compared to the control group of Alzheimer's subjects may derive from a selection bias of a cohort of Alzheimer's patients with COVID-19 casually characterized by a more relevant Alzheimer's β-amyloidopathy before SARS-CoV-2 infection. Moreover, a detailed report of clinical features (e.g. history and symptoms) of COVID-19 patients and control subjects is lacking.

Given their results showing no effect on the increase of intracellular neurofibrillary tangles (as evident from panel H of Figure 4), how do the authors explain the Alzheimer's-like behavior of SARS-CoV-2 infection, which apparently would only act on BACE-1-dependent β-amyloid cascade?

The authors should discuss and comment on several studies that have suggested an indirect effect rather than a direct invasion of SARS-CoV-2 infection in determining brain pathology abnormalities.

Furthermore, I have some concerns regarding some statistical analyses. Indeed, in the legends of Figures 4, 6, 7, and S4, the authors have declared that the Mann-Whitney test was used after confirming a normal distribution. This statement deserves a proper explanation since the Mann-Whitney test is a non-parametrical test, which is applied to data that is not normally distributed. Also, in Figures 6 and 7, when more than two groups are compared, the authors should use the Kruskal-Wallis test as a non-parametrical analysis followed by a posthoc test, instead of a Mann-Whitney test (similarly to ANOVA with posthoc Tukey as parametrical analysis).