Omicron BA.5 is neuroinvasive and lethal in K18-hACE2 mice.

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Background: Neurological sequelae represent a major component of COVID-19 and long COVID. Infection of K18-hACE2 mice with original ancestral isolates, results in fulminant and lethal brain infections. Interestingly, the omicron BA.1 exhibits reduced brain infection and mortality in K18-hACE2 mice suggesting a potential link between brain infection and mortality. It is currently unclear whether newer variants of SARS-CoV-2 are also neurotropic and contribute to the attenuated pathogenicity observed with omicron BA.1. We therefore investigated the pathogenicity of a BA.5 isolate in K18-hACE2 mice, and the relationship with neuroinvasion and neurotropism.

Methods: K18-hACE2 mice and human cortical organoids were infected with an original (ancestral) strain, omicron BA.1, or omicron BA.5 isolate, and control mice inoculated with UV-inactivated BA.5. Mouse brains and human cortical organoids were collected for immunohistochemistry and RNA sequencing.

Results: Herein we demonstrate that a BA.5 isolate is as lethal as the original strain and is also both neuroinvasive and neurotrophic. IHC staining of brains of K18-hACE2 mice infected with BA.5 showed widespread infection in the cortex, as well as the hippocampus and the hypothalamus. We used co-staining with the neuronal marker NeuN and SARS-CoV-2 S-protein demonstrating that neurons are the primary target cells in K18-hACE2 mouse brains. Interestingly we found no signs of infection of microglia labelled with Iba1 or astrocytes labelled with GFAP. We also demonstrate that omicron BA.5 infected human cortical organoids at a higher rate than the original ancestral virus. Finally, bioinformatic analyses demonstrate that BA.5-infected K18-hACE2 mouse brains show typical SARS-CoV-2-associated inflammatory responses and activation of microglia.

Conclusion: These results argue that while omicron virus may be associated with reduced respiratory symptoms, BA.5 shows increased neurovirulence compared to earlier omicron sub-variants.

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