Identifying the neurological impact of COVID-19 in a mouse of model of SARS-CoV-2 infection

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Background: The long-term health outcomes of brain injury arising from infection with SARS-CoV-2 are yet to be realised. Understanding the pathogenesis of acute and chronic (long) neurological symptoms of COVID-19 is essential to developing effective interventions. Mouse models of infection can be used to assess neural invasion and pathology of acute viral infection, study the long-term health outcomes and identify and test therapeutic targets. We have used a naturally mouse tropic variant of SARS-CoV-2 to infect wildtype mice to assess the acute and long-term neurological impact of COVID-19.

Methods: The mouse tropic VIC2089(N501Y) isolate of SARS-COV-2 was identified though computational prediction of docking to murine ACE2 and shown to induce a productive respiratory infection and disease in wildtype mice. The neurological phenotype of this isolate was compared to the ancestral VIC01 isolate in cultures of human neurons (SH-SY5Y), astrocytes (U87) and microglial (HCM3) cells and neural invasion and neuropathology of VIC2089(N501Y) was assessed in wild-type mice following intranasal infection.

Results: In vitro VIC01 and VIC2089(N501Y) had a similar neurological phenotype with viral RNA detected in neurons, astrocytes and microglia 48 hours after infection and evidence of viral replication and IL-6 production in neurons. Following intranasal infection of wildtype mice with VIC2089(N501Y) pathology consistent with a vacuolating encephalitis was detected in the brain of adult (10 week) and aged (6 month) mice during the acute respiratory infection which persisted for at least 14 days post inoculation and after clearance detectable respiratory infection.

Conclusion: This natural model of COVID-19 associated brain injury will be used to assess routes of SARS-CoV-2 neural invasion, identify the mechanism of infection associated brain injury, assess the long-term health and behavioural outcomes of infection and identify and test the efficacy of therapeutic interventions.