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Neuronal Death and Inflammation in Brain of SARS-CoV-2 Infected Non-Human Primates

Introduction: Neurological manifestations are a significant complication of syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus infection disease-19 (COVID-19). These likely contribute to post-acute sequalae of COVID-19 (PASC) or “long COVID”. Understanding how infection contributes to neuropathogenesis is needed for appropriate treatment of infected patients, as well as in initiating relevant follow-up care after recovery. Brain autopsy series of human subjects who died from COVID-19 have revealed significant pathology, including wide-spread neuroinflammation and microhemorrhages. In this report, we show for the first time, neuropathology in SARS-CoV-2 infected non-human primates (NHPs) that is consistent with that reported among human patients. **Methods:** Eight adult NHPs were inoculated with the 2019-nCoV/USA-WA1/2020 strain of SARS-CoV-2 via a multi-route mucosal or aerosol challenge. Immunohistochemistry staining was done on seven brain regions, including frontal, parietal, occipital, and temporal lobes, basal ganglia, cerebellum, and brainstem to elucidate the presence of platelet derived thrombi, neuronal apoptosis, and virus present. General pathology and microhemorrhages were examined on hematoxylin and eosin-stained (H&E) tissues. **Results:** Similar to humans, pathology was variable but included wide-spread neuroinflammation, nodular lesions, neuronal degeneration, and microhemorrhages. Changes in

neuronal morphology suggestive of neuronal degeneration were identified with H&E staining and most often seen in the cerebellum and brainstem of infected animals. Neuronal death was confirmed through FluorJade C and cleaved (active) caspase 3 IHC, which showed foci of positivity, particularly among Purkinje cells of the cerebellum. Importantly, this was seen among infected animals that did not develop severe respiratory disease. Sparse virus was detected in brain endothelial cells but did not associate with the severity of CNS injury. **Conclusions:** We anticipate our findings will advance our current understanding of the neuropathogenesis of SARS-CoV-2 infection and demonstrate SARS-CoV-2 infected NHPs are a highly relevant animal model for investigating COVID-19 neuropathogenesis among human subjects.