Abstract Information

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Title :	Neuropathological Impacts of Pre-Injury Stress in Ferrets (Mustela putorius furo) with Traumatic Brain Injury (TBI)

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Abstract :

Background & Objectives: Traumatic Brain Injury (TBI) leads to significant disability and death, and is linked to neurodegenerative diseases and sleep disorders. Sleep activates the glymphatic system, which removes brain metabolites via aquaporin-4 (AQP4) channels. Chronic stress disrupts this process, leading to sleep disorders and exacerbating stress, which negatively impacts health. Despite the intrinsic relationship between stress and TBI, few studies have explored the influence of pre-existing stress on TBI outcomes. This study investigated the impacts and temporal dynamics of pre-injury stress exposure in ferrets with TBI, focusing on activity/sleep patterns, components of the glymphatic system and various neurological markers. Methods: Adult male ferrets were divided into three cohorts (C1, C2, C3) and assigned to Control, Injury (IN), or Injury+Stress (I+S) groups. Each cohort underwent different injury and stress protocols. Activity/sleep patterns were monitored. Brain tissue was analysed using immunofluorescent markers for astrocytes, AQP4 and microglia. Results and Discussion: At 1MPI, CON exhibited distinct clusters of sustained high-activity with 50% being significantly active for over 50 minutes. Clustering was greatly reduced and more random in IN and I+S. At 6MPI, I+S had more high activity clusters than IN but e less sustained and more random than CON. Changes in activity patterns inferred sleep disturbances, with reduced activity indicating potential fatigue and reduced functionality. Elevated astrocytic and AQP4 immunoreactivity persisted in IN and I+S up to 6MPI. An important feature of TBI is reactive astrogliosis and an upregulation of AQP4 expression, impacting neuroinflammation, sleep

regulation, post-traumatic oedema and secondary injury progression. IN exhibited microglial activation at 1MPI, transitioning to amoeboid morphology by 6MPI. I+S showed reduced microglial immunoreactivity compared to IN. Chronic microglial activation contributes to secondary injury and chronic neurodegenerative pathology after TBI. Stress seemed to reduce IBA1 immunoreactivity, with previous studies showing chronic stress elevates microglia in stress-sensitive brain regions and shifts them to an active state. In conclusion, pre-existing stress can influence TBI outcomes over time, affecting activity/sleep patterns, astrocytic reactivity and microglial response. Paradoxically, pre-injury stress showed some neuroprotective effects in TBI, highlighting the complex relationship between stress and brain injury outcomes. Keywords- TBI, Ferrets, Stress