The role of tau and other pathologies in an animal model of repetitive mild traumatic brain injury.

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Background:

The Chronic Effects of Neurotrauma Consortium or CENC is dedicated to understanding the chronic sequelae associated with neurotrauma, primarily focused on mild TBI (mTBI)/concussion incurred by U.S. service personnel. To enable a detailed assessment of TBI sequelae and potential development of neurodegeneration and other comorbidities, a mouse model of repetitive mild TBI (r-mTBI) was developed to track the underlying pathobiology and behavioral dysfunction associated with r-mTBI over time. In addition to neurodegeneration and cognitive impairment, TBI is occasionally associated with a progressive tauopathy, chronic traumatic encephalopathy (CTE). Mounting evidence suggests aberrant tau processing or hyperphosphorylation contributes to the development of CTE. However, little is known about the timeline and sequence in which tau is processed following TBI, nor about the relationship with other TBI-dependent neuropathologies such as neuroinflammation and cerebrovascular changes. This study will evaluate tau alterations and accompanying neuropathologies over time after r-mTBI in hTau transgenic mice.

Methods:

hTau mice (expressing all six isoforms of human tau) aged either 8-12 weeks will receive either r-mTBI (five hits with an inter-injury interval of 48hrs) or r-sham in order to control for the effects of repeated anesthesia. Mice will be euthanized for neuropathological, genomic and biochemical analyses at 24hrs, 5, 10 and 15 days, 3, 6 and 12 months after last mTBI/anesthesia. For the 15 day and 3, 6 and 12 month time points post injury mice will undergo a battery of neurobehavioral test in the 2 weeks immediately prior to euthanasia. The entire paradigm will be replicated in hTau mice aged 12 months at the time of injury, to study the effects of age at time of injury.

Results:

r-mTBI in the young cohort shows learning impairment post injury that progressively worsens from 2 weeks to 12 months. To date, Tau IHC and ELISA results suggest that r-mTBI is associated with a transient injury dependent increase in p-tau accumulation with greater dendritic and membranous staining in the cerebral cortex beneath the impact site. It is worth noting that the nature of the tau pathologies observed in our model do not show neurofibrillary tangles, which is a key finding in autopsied human brains with a history of repetitive TBI. While a trend for an increase in aggregated tau at 12 months post injury was observed, r-mTBI was not associated with elevated brain levels of abnormal soluble tau phosphorylation. This study is ongoing and will take several years to complete; our previous data suggest that neuroinflammatory pathology is key in this model and that TBI-dependent tau pathology will be evident in the older mouse models where tau pathology already exists.

Conclusion:

The data suggest that increased p-tau immunoreactivity appears to be transient in this model of r-mTBI. While the increase of p-tau may play a role in the acute behavioral changes post injury, it does not account for the behavioral changes observed at 12 months post injury. Additional prospective studies will continue to evaluate the role of tau in TBI sequelae.