Lower Motor Neuron Degeneration Following Traumatic Brain Injury

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Introduction

A traumatic brain injury (TBI) is defined as an injury to the head that disrupts the normal function of the brain. In 2013 alone, there were approximately 2.8 million TBI related emergencies reported in the United States consisting of ~2.5 million emergency room visits, 282,000 hospitalizations, and 56,000 deaths. Primary injuries of TBI result in immediate cell death and disruption of normal functionality. Presently, there are no standardized treatments or cures for a TBI primary injury besides symptomatic treatments and supportive therapies. Secondary injuries however result in a complex biochemical process that can lead to cognitive impairments and a greatly increased risk for the development of several chronic neurodegenerative disorders. In this sense, TBIs can be described as a disease process that only begins with the primary injury.

Currently there is some debate as to the role of TBIs and the future development of neurodegenerative disease such as frontotemporal lobar degeneration (FTLD) and motor neuron diseases (MNDs) such as amyotrophic lateral sclerosis (ALS). In this study, we plan to analyze the relationship between a TBI and the development of MNDs using immunohistochemical markers of proteinopathies in a post TBI animal model.

Objective

The goal of this research project is to explore the effects of a single traumatic brain injury (TBI) on lower motor neuron (LMN) loss and degeneration. The primary injury site of the TBI is focused on the primary motor cortex of the brain. Motor neurons of this area primarily send neural impulses to the cervical spinal cord that controls proximal and distal forelimb motor control. This area of the spinal cord will allow the analysis of downstream neurodegenerative effects due to the TBI primary injury.

Experimental Methods

Our current preliminary data was collected from wild-type C57BL/6J mouse cervical spinal cords and prefrontal cortex of wild-type Long-Evans rats. Injuries were performed using a stereotaxic mounted impactor centered over the primary motor cortex of the left cortical hemisphere after performing a 4mm diameter craniotomy. Injury impact was controlled at 2mm diameter X 1mm depth for mice and 3mm diameter X 2mm depth for rats. Following TBI and recovery, animals were sacrificed at specified time points by transcardial perfusion with ice-cold PBS followed by ice-cold 4% PFA. Brains and spinal cords were dissected and prepared for immunohistochemical analysis.

Preliminary Finding – ALS-like MND

Cervical spinal cord of naive control and 28 days post injury mice. Representative spinal cord sections stained for TDP-43 and NEUN (RBFOX3) which is used commonly as a neuronal marker. Interestingly, NEUN is an RNA binding protein involved in the alternative splicing of RNA that appears to exhibit a similar localization pattern that is seen in TDP-43.

These sections exhibit a similar translocation of TDP-43 from the spinal cord motor neurons nucleus in the injured animals with aggregations forming in the cytoplasm (yellow areas). Additionally, there further appears to be a distinct difference between the two sides of the spinal cord in the injured animal alone. Each side represents connectivity to the injured and uninjured hemispheres of the cortex (n=1).

Acknowledgments and References

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References