Exosomal and Plasma Protein Biomarkers of Neuronal Injury and Inflammation in Chronic Mild TBI: A Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project

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Objective: To profile plasma and exosomal protein levels as candidate biomarkers of chronic traumatic brain injury (TBI) among veterans with mild TBI (mTBI) in the Chronic Effects of Neurotrauma Consortium (CENC).

Background: Chronic symptoms and disabilities after mTBI are common. Blood-based proteins, including exosomal, are increasingly recognized for their potential to improve diagnosis, prognosis, and treatment of acquired neurological and neurodegenerative disorders. Few studies have evaluated biomarkers in chronic TBI, especially > 6 months after injury.

Design/Methods: Exosomal and plasma levels of tau, phosphorylated tau (p-tau), amyloid beta 40 (Aβ40), amyloid beta 42 (Aβ42), neurofilament light (NFL), vascular endothelial growth factor (VEGF), tumor necrotizing factor alpha (TNFa), Interleukin-6 (IL-6) and Interleukin-10 (IL-10) were measured in a cohort of 195 Veterans [150 with mTBI, 56 with ≥3 mTBIs (rTBI)], from the CENC Longitudinal Study. We assessed the relationship between biomarkers and post-concussive (PC), post-traumatic stress (PTSD) and depressive symptoms using the NSI, PCL and PHQ-9 scales, respectively. Biomarker levels were compared between groups with and without mTBI, and among those with no TBI (controls), 1-2 mTBIs and rTBI.

Results: Exosomal tau, p-tau, NFL, IL-6 and IL-10 as well as plasma NFL, tau, IL-6 and IL-10 were significantly elevated in rTBI compared to those with 1-2 mTBIs. Additionally, total number of TBIs correlated with exosomal IL-6, IL-10 and both exosomal and plasma NFL levels. The number of TBIs associated with blast exposure correlated with exosomal IL-6. NSI, PCL and PHQ-9 scores each correlated with exosomal tau, p-tau, IL-6 and NFL.

Conclusions: rTBI is associated with elevated peripheral exosomal levels of NFL, tau, p-tau, IL-6 and IL-10. Exosomal tau, p-tau NFL and IL6 are each variably associated with PC, PTSD and depression symptoms, suggesting exosomal signaling may play a role in chronic mTBI pathophysiology and support the use of peripherally circulating exosomes as biomarkers in chronic mTBI.