

A06-10

CSF BIOMARKER LEVELS OF A β 40 AND TAU/A β 42 CORRESPOND TO NEUROPSYCHOLOGICAL OUTCOME IN CHRONIC TBI PARTICIPANTS

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Objectives: Traumatic brain injury (TBI) involves axonal injury and accumulation of pathological protein aggregates including amyloid- β (A β) and hyperphosphorylated tau (p-tau). Biomarker analysis of tau and A β concentrations in cerebrospinal fluid (CSF) may be an objective marker of cognitive status after TBI. The goal of the current study was to analyze tau and A β 40–42 in a cohort of military and civilian participants with chronic deficits secondary to TBI, and correlate neuropsychological outcome data with concentrations of tau and A β 42 measured in CSF from the same subjects.

Methods: 19 chronic TBI participants (> 6 months from injury; 16 males, mean age 41yrs, 8 military veterans and 11 civilians) underwent lumbar puncture as well as neuropsychological testing. CSF was analyzed for concentrations of total tau, A β 1–42 (A β 42) and A β 1–40 (A β 40) by ELISA, and tau/A β 42 ratio was calculated. The neuropsychological test battery included measures of memory, processing speed and executive function: California Verbal Learning Test-II (CVLT) Short and Long Delay Free Recall (SDFR, LDFR), Wechsler Adult Intelligence Scale Working Memory Index (WAIS IV) and Trail Making Test Part A/B. Nonparametric correlation (Spearman rho, ρ) was used to relate CSF levels to neuropsychological data, controlling for age.

Results: CSF tau/A β 42 ratio was inversely associated with Trails B (Spearman $p > -0.49$, $p < 0.047$). CSF A β 40 concentration was inversely correlated with CVLT SDFR and LDFR (Spearman $p > -0.51$, $p < 0.032$; $p > -0.50$, $p < 0.034$, respectively). There were no significant correlations between CSF biomarker levels and WAIS neuropsychological measures.

Conclusions: In chronic TBI, neuropsychological outcome on measures of memory and executive function (CVLT and Trails B) corresponded to CSF biomarkers of tau and A β concentrations. Additional studies with a larger cohort of TBI participants are needed to draw meaningful conclusions. The use of CSF biomarkers in ongoing studies will allow us to test more specific hypotheses regarding the link between TBI and chronic neurodegenerative conditions such as chronic traumatic encephalopathy.

Keywords: chronic TBI, amyloid B, tau, neuropsychological outcome

A06-11

SGP130 MODERATES THE RELATIONSHIP BETWEEN CHRONIC IL-6/SIL-6R COMPLEX IN DIFFERENTIATING OUTCOME AFTER SEVERE TBI

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The secondary injury response after traumatic brain injury (TBI) is characterized by an acute innate immune response. While research has focused on acute neuroinflammatory markers, our previous work suggests sub-acute and chronic peripheral inflammatory markers influences long-term global outcomes. Specifically, pro-inflammatory mediators,

including interleukin 6 (IL-6), 2 weeks to 3 months post-injury, were associated with worse global outcomes at 6 and 12 months. Further, the relationship between IL-6 and its soluble receptor, sIL-6R, facilitates a signaling cascade predisposing individuals to a chronic inflammatory state; in contrast soluble gp130 (sgp130), a potent IL-6 inhibitory transmembrane protein, moderates this relationship. To date, no clinical or experimental TBI study has examined the association between IL-6/sIL-6R and sgp130. The objective of this study was to evaluate relationships between serum IL-6, sIL-6R, and sgp130 in the subacute period post-injury for N=100 individuals with severe TBI. Monthly ratios were produced for IL-6: sIL-6R and sgp130:sIL-6R, and IL-6 levels were quartiled using levels from samples collected up to 3 months post-injury. Six-month GOS scores were dichotomized to reflect poor (GOS=2/3) vs. good (GOS=4/5) outcome. Bivariate analysis showed significant differences in sIL-6R by GOS group ($p < 0.0001$), where higher sIL-6R levels were associated with poor outcome. sgp130:sIL-6R ratios also significantly differed by GOS group ($p = 0.0034$), where lower ratios were associated with poor outcome. A multivariate logistic regression model including age, IL-6, sgp130:sIL-6R, and a sgp130:sIL-6R*IL-6 resulted in a significant interaction (OR=5.527, $p = 0.0047$) in predicting 6-month outcome. The interaction suggests sgp130:sIL-6R ratios influence global outcome by attenuating the IL-6/sIL-6R complex, resulting in higher IL-6 levels. These results suggest the preferential binding of sgp130 to sIL-6R selectively blocks progression of inflammation through the inhibition of IL-6 signaling by the sIL-6R after severe TBI. This work has novel implications for understanding how sgp130 potentially serves as a modifiable target for prevention and/or resolution of chronic inflammation post-TBI. Support: DoD-W81XWH-071-0701; NIDILRR-90DP0041; R49-CCR323155.

Keywords: chronic inflammation, traumatic brain injury, innate immunity, interleukin 6, sgp130

A06-12

PHARMACOLOGICAL MRI TO PROBE NMDA-MEDIATED CIRCUIT CHANGES IN THE IMMATURE RAT AFTER FPI

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Hippocampal lateral fluid percussion injury (LFPI) has been previously correlated with memory and recognition deficits in developing rats and dysfunction of glutamatergic neurotransmission via the N-methyl-D-aspartate receptor (NMDAR), is a plausible factor. Protein expression studies have confirmed a downregulation of NMDAR protein after experimental traumatic brain injury (TBI). To study the dynamics of NMDARs in vivo, and their role in memory-related network dysfunction after developmental TBI, we acquired pilot pharmacological magnetic resonance imaging (phMRI) data at day 4 following injury (n=6) or sham (n=4) of post-natal day-19 rats. This included a 5 minute baseline Cerebral Blood Volume (CBV) enhanced imaging (7T Bruker spectrometer using a single-shot, gradient-echo sequence, echo/repetition time: 20/1000ms, 300 repetitions, 128×128 matrix, 30×30mm field-of-view and 1mm slice-thickness) followed by systemic injection of 30 mg/kg DCS/ Saline in a 1×4 experimental design. Image acquisition continued 15 minutes post-injection. After typical preprocessing of time-series data and standard space registration, Region of Interest (ROI) based rCBV response analysis (pre vs. post drug challenge) was then performed for five brain regions identified in a prior study as the memory and recognition circuit, Prefrontal Cortex (PFC); Hippocampus (Hip); Thalamus (Tha); Perirhinal (PRh) and Entorhinal (Ent) cortex. No significant changes in regional CBV signal were observed

in control animals following the saline injection. Regional CBV percent signal changes showed DCS-modulated network activation (PFC: +2.29; Ent: +2.64; Hip: +3.46; Prh: +3.05; Tha: +2.99) in sham control rats. Injured brain responses to the DCS challenge were in agreement with our hypothesis of injury induced hippocampal neural network irregularities (PFC: +0.85; Ent: +0.20; Hip: 0.90; Prh: +1.12; Tha: +1.34). Perceived NMDAR-modulated responses were then fed into a multivariate Granger causality analysis which also confirmed the existence of significant ($p < 0.01$) changes in the DCS-mediated hippocampal neural network between injury and sham.

Funding: R01NS27544, R01NS091222, UCLA Easton Labs for Brain Injury, UCLA Steve Tisch BrainSPORT program, UCLA BIRC.

Keywords: Pharmacological MRI, Developmental TBI, NMDA receptor, D-Cycloserine, Bain Connectivity Network

A06-13

ASSOCIATION OF RELEASED TISSUE FACTOR WITH ELEVATED D-DIMER AS A SERUM BIOMARKER OF TRAUMATIC BRAIN INJURY

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Objective: Recently, D-dimer blood levels were reported as a biomarker for the outcome of traumatic brain injury (TBI) patients. However, the mechanisms that trigger elevated D-dimer blood levels in TBI remain unclear. The purpose of this study was to evaluate the reliability of D-dimer as a biomarker of TBI and to determine the mechanisms involved in regulating its blood levels.

Methods: Nine patients with moderate to severe (Glasgow Coma Scale score 3-13) isolated TBI were admitted and evaluated at our hospital between May 2013 and June 2014. We collected blood samples from systemic arteries on arrival in the emergency room and at 1, 3, 5, 7, and 14 days after injury. The plasma levels of neuron specific enolase (NSE), D-dimer, and soluble tissue factor were measured.

Results: The plasma levels of NSE (33.4 ng/ml: normal value less than 12.0 ng/ml) and D-dimer (56.1 μ g/ml: normal value less than 1.0 μ g/ml) were elevated on admittance and declined but were still elevated on Day 1 after injury. A significant correlation between NSE and D-dimer was seen on admittance ($R = 0.727$, $p = 0.026$) and on the following days ($R = 0.694$, $p < 0.001$). Furthermore, a significant correlation between soluble tissue factor and D-dimer was seen on admittance ($R = 0.803$, $p = 0.009$).

Conclusion: The level of blood D-dimer accurately reflected the degree of brain damage indicated by NSE levels. Our data suggest that the release of tissue factor induced by brain damage may activate the coagulation cascade leading to elevation in D-dimer levels.

Keywords: traumatic brain injury, coagulopathy, biomarker

A06-14

ASTROGLIAL CELL WOUNDING BIOMARKER ALDOLASE C IS ROBUSTLY ELEVATED IN MILD TBI PATIENTS

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Diagnostic monitoring of mild traumatic brain injury (mTBI) requires robust biomarkers for precise, sensitive, objective assessment. We recently identified Aldolase C (ALDOC) as a protein released from acutely traumatized astrocytes *in vitro* (Levine et al., 2016). GFAP release and proteolysis was associated with delayed cell death, dependent on injury severity (Halford et al., accepted). The current study examined ALDOC and GFAP levels in clinical samples after TBI. Healthy controls, mTBI, severe TBI and athletic cohorts were studied in replicate electrochemiluminescence-based ELISAs and compared with detectable protein bands in standardized immunoblotting assays. Rank Sum, permutation and paired T-tests were used to measure significant differences between cohorts. Studies demonstrated the C-isoform specificity of the antibodies and showed CNS-specific expression. Both assays confirmed ALDOC elevation after TBI compared to healthy controls (all reported comparisons were significant at $\alpha = 0.05$). A cohort of Italian mTBI patients showed serum ALDOC elevation irrespective of CT-status, while GFAP levels rose only in CT+ mTBI. In HeadSMART mTBI patients, ALDOC was significantly elevated versus healthy controls. ALDOC levels rose significantly in concussed NCAA athletes after injury, versus controls and non-concussed players. In Israeli football players, ALDOC elevation, but not GFAP, was detected in concussed players versus controls. ELISA testing and immunoblotting for GFAP breakdown-products found no GFAP elevation in either athlete study despite elevation in severe TBI and some mTBI patients. Overall, multiple mTBI cohorts of different age, athletic groups, and geographical location support ALDOC as a robust biomarker for mTBI.

Keywords: Biomarker, GFAP, ALDOC, Athlete, mild TBI

A06-15

EXAMINING ADAPTIVE IMMUNE RESPONSE AND RELATIONSHIPS BETWEEN IL-7 AND ANTI-PITUITARY/HYPOTHALAMIC AUTOANTIBODIES AFTER SEVERE-TBI

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Traumatic brain injury (TBI) is associated with long-term complications, including persistent hypogonadotropic hypogonadism (PHH), which our studies suggest a link to autoimmunity. Autoantibodies (AAb) to the pituitary (APA) and hypothalamus (AHA) are present up to one-year following TBI and reduced IgM AAb increases PHH-risk among men with TBI. Adaptive immunity, including interleukin 7 (IL-7) production, may promote brain tissue-specific AAb