**Characterization of Metabolic Profiles of Adult Severe Traumatic Brain Injury**

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**Introduction:** Traumatic brain injury is a leading cause of death and disability worldwide. Diagnosis of mild TBI (mTBI) and prognosis of severe TBI (sTBI) have proven to be particularly challenging. The use of biomarkers as tools for diagnosis and prognosis of TBI have not been useful to date. We and others believe that metabolomics may be a promising approach to develop more sensitive and specific biomarkers in TBI through the assessment of metabolite changes in biofluids. We used nuclear magnetic resonance (NMR) and mass spectrometry (MS) techniques to identify and quantify metabolites to examine their use in sTBI diagnosis and prognosis.

**Methods:** 58 patients with sTBI (GCS ≤ 8) and 35 age- and sex-matched orthopedic injury (OI) control patients (without brain injury) were enrolled in this study. Serum samples were drawn on the 1st and 4th day post injury from patients with sTBI and on the 1st day post injury from OI controls. We applied a targeted quantified DI-MS/MS analysis for metabolomics profiling of the serum samples. Multivariate and univariate data analyses were applied to analyze the metabolomics profiles of sTBI and OI control cohorts.

**Results:** 130 metabolites including lipids, amino acids, biogenic amines and organic acids were quantified using DI-MS/MS of serum samples. As compared to OI control patients serum metabolomics profiles of sTBI patients at both day 1 and day 4 were different, with the magnitude of the difference greater at day 4, in highly predictive models (Q²>0.7) (Figs. 1 & 2 & 3). Moreover, day 1 serum sTBI metabolites were significant different that day 4 with a highly predictive OPLS-DA model (Q²=0.672). Univariate analysis also showed that multiple metabolites differed significantly in concentration (FDR< 0.05) between the sTBI and OI groups.

**Discussion:** Our study shows that there are significant differences in quantified metabolites levels between patients with sTBI (on days 1 and 4) and OI control patients. Additionally, the serum metabolomics profiles are significantly different as a function of time post-injury which may reflect primary and secondary brain injury changes on metabolites that needs to be explored further.
Figure 1. OPLS-DA prediction model to show the separation of day 1 serum samples of sTBI patients vs OI control patients. $Q^2=0.756$ and $p=1.2e-22$ show a highly predictive and significant model to differentiate sTBI from OI control using 49 metabolites.

Figure 2. OPLS-DA prediction model to show the separation of day 4 serum samples of sTBI patients vs OI control patients. $Q^2=0.79$ and $p=1.1e-23$ show a highly predictive and significant model to differentiate sTBI from OI control using 46 metabolites.

Figure 3. PCA analysis shows that the metabolic profiles of sTBI patient serum at day 4 is different than serum of sTBI patients at day 1 when compared to the OI controls.

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