Brain Injury Diagnostics

Cerebrospinal Fluid Biomarkers Corresponding to Memory and Executive Function in Chronic Traumatic Brain Injury

Trauma-associated neurodegenerative diseases, including Chronic Traumatic Encephalopathy (CTE), continue to generate significant interest, but have many unanswered questions relating to: onset, progression, timing of pathological changes, and degree of association with traumatic brain injury (TBI). In the case of CTE, diagnosis is, at present, only possible at autopsy, as there is no current method for effective detection in living persons. Recent military conflicts have resulted in a significant military population with TBI or exposure to concussive and subconcussive blast forces. The process of neurodegeneration typically occurs at longer timescales following TBI and is, to the best of our knowledge, irreversible. Thus, there is a pressing need to understand TBI-associated neurodegeneration, understand the contribution of TBI to risk of decline, and develop diagnostic markers to detect neurodegeneration earlier in life.

The proteins A-beta and tau have been implicated in a number of neurodegenerative diseases, including CTE, and represent a promising lead in developing accurate in vivo diagnosis. Researchers at the University of Pittsburgh (Pittsburgh, Pennsylvania) have been developing a neuroimaging- and blood-based biomarker panel that can detect CTE in individuals with a history of TBI and at risk for developing a neurodegenerative disease. This work involves the use of positron emission tomography (PET) imaging markers for A-beta and tau, and an enzyme-linked immunosorbent assay (ELISA) of cerebrospinal fluid (CSF) in participants with chronic TBI (Military, Veteran, and civilian) from the Pittsburgh Targeted Evaluation, Action, and Monitoring of Traumatic Brain Injury clinical trial. A central goal of this work is to understand the linkage between A-beta and tau and persistent cognitive impairments.

In preliminary work presented at the 2017 Military Health System Research Symposium, the study team reported that neuropsychological outcome on measures of memory and executive function corresponded to cerebrospinal fluid (CSF) biomarkers of tau and A-beta concentrations (*Puccio et al. 2017*). Of 19 chronic TBI participant (>6 months of injury), CSF tau/Amyloid Beta 42 (Aβ42) ratio was inversely associated with Trails B testing (Spearman $p > -0.49$, $p < 0.047$) and CSF Aβ40 concentration was inversely correlated with California Verbal Learning Test Short Delay Free Recall and Long Delay Free Recall results (Spearman $p > -0.51$, $p < 0.032$; $p > -0.50$, $p < 0.034$, respectively).

Two patients were identified with significant cognitive sequelae in the chronic phase of TBI. Both patients (Figures 1 and 2) demonstrated decreased regional glucose metabolism ([^{18}F] fluorodeoxyglucose-positron emission tomography.) (D) in posterior brain regions and global increased amyloid deposition (uptake of [^{11}C] PiB) (C) in a pattern similar to that demonstrated in Alzheimer's Disease. The pattern of [^{18}F] AV-1451 uptake (B) is most prominent in occipital, parietal, and temporal lobes in both patients. This pattern is similar to the uptake of other tau-specific radiotracers that have been studied in patients

with suspected CTE. It is also in agreement with the neuropathological findings of tauopathy in autopsy specimens of patients with advanced, stage IV CTE.

In summary, development of biomarker panels and assays for CTE will enable earlier diagnosis of TBI-associated neurodegenerative diseases in living subjects and inform potential treatment strategies and therapeutic targets for chronic TBI.

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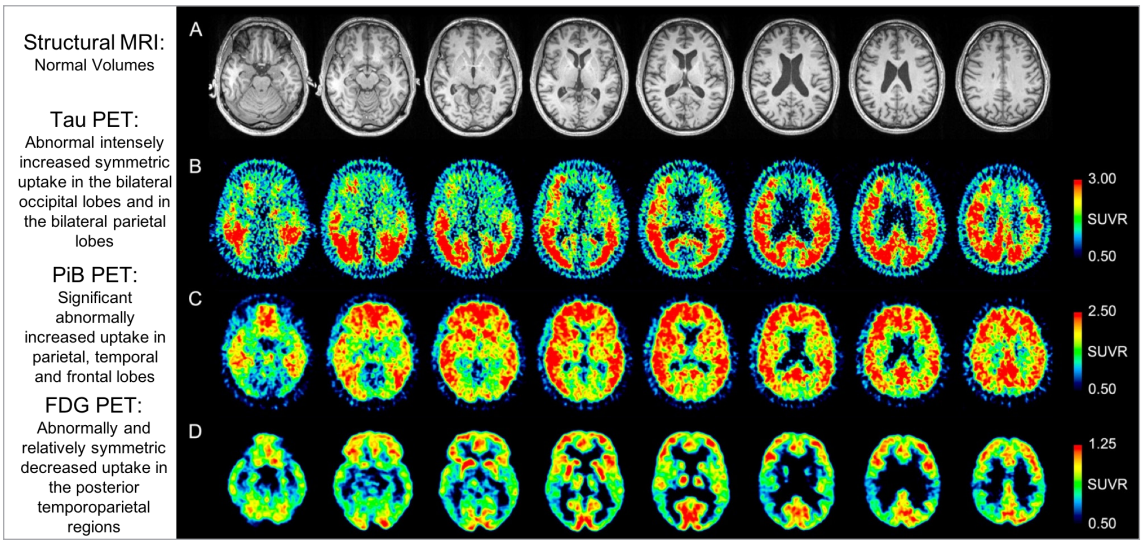

FIGURE 1: Case 1: Navy explosive ordinance Veteran with history of both blunt head trauma and numerous blast-related TBI. (Figure used with permission from the authors)

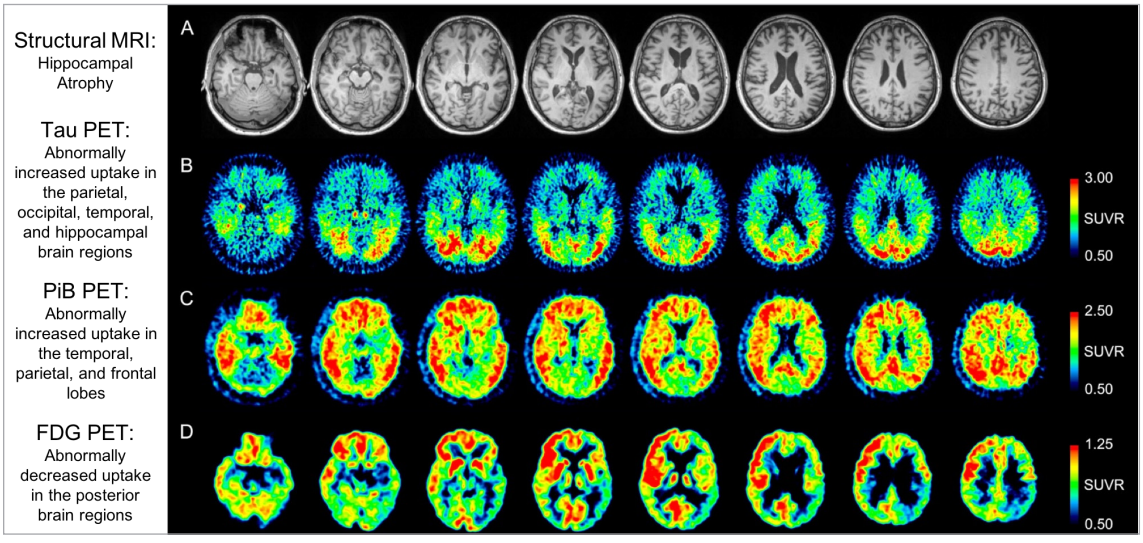

FIGURE 2: Case 2: individual with long-standing history of numerous sports-related concussions. (Figure used with permission from the authors)

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