ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2016) 1-8

Alzheimer's & Dementia

Repetitive head impact exposure and later-life plasma total tau in former NFL players

Michael L. Alosco[a,b], Yorghos Tripodis[a,c], Johnny Jarnagin[a], Christine M. Baugh[a,b,d], Brett Martin[a,e], Christine E. Chaisson[a,c,e], Nate Estochen[f], Linan Song[f], Robert C. Cantu[a,b,g], Andreas Jeromin[f], Robert A. Stern[a,b,g,h,*]

[a]*Boston University Alzheimer's Disease and CTE Center, Boston University School of Medicine, Boston, MA, USA*
[b]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[c]*Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA*
[d]*Interfaculty Initiative in Health Policy, Harvard University Boston, MA, USA*
[e]*Data Coordinating Center, Boston University School of Public Health, Boston, MA, USA*
[f]*Quanterix Corporation, Lexington, MA, USA*
[g]*Department of Neurosurgery, Boston University School of Medicine, Boston, MA, USA*
[h]*Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA*

Abstract

Introduction: Blood protein analysis of total tau (t-tau) may be a practical screening biomarker for chronic traumatic encephalopathy (CTE), a neurodegenerative tauopathy associated with repetitive head impact (RHI) exposure. We examined plasma t-tau in symptomatic former NFL players compared with controls and the relationship between RHI exposure and later-life plasma t-tau.

Methods: Ninety-six former NFL players (age 40–69) and 25 same-age controls underwent blood draw to determine plasma t-tau levels. The cumulative head impact index (CHII) quantified RHI exposure. Subjects completed measures of clinical function.

Results: A higher CHII predicted greater plasma t-tau in the former NFL players ($P = .0137$). No group differences in plasma t-tau emerged, but a concentration $\geq$3.56 pg/mL was 100% specific to former NFL players. Plasma t-tau did not predict clinical function.

Discussion: Greater RHI exposure predicted higher later-life plasma t-tau concentrations, and further study on plasma t-tau as a candidate screening biomarker for CTE is warranted.

Keywords: American football; Chronic traumatic encephalopathy; Repetitive head impacts; Tau; Total tau; Plasma; Head trauma

1. Background

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease only found in individuals with a history of exposure to repetitive head impacts (RHIs), such as former American football players [1,2]. The pathognomonic lesion of CTE is the perivascular deposition of hyperphosphorylated tau (p-tau) at the depths of the cortical sulci [3]. P-tau deposition is initially seen in frontotemporal brain regions, progresses to the medial temporal lobes (MTLs), and eventually becomes widespread. CTE presents with a constellation of cognitive, behavior, and mood deficits and, in some cases, motor signs [4]. Although CTE can only be diagnosed by neuropathological examination [3], clinical research diagnostic criteria have been proposed [5]. Yet, in vivo biomarkers that can detect the presence of CTE pathology during life have not yet been identified, precluding the ability to accurately diagnose CTE at this time. Biomarkers have become the gold standard in the diagnosis of neurodegenerative diseases,

*Corresponding author. Tel.: 617-638-5679; Fax: 617-638-5678.
E-mail address: bobstern@bu.edu

http://dx.doi.org/10.1016/j.dadm.2016.11.003

such as Alzheimer's disease (AD), and play a key role in understanding disease biology and determining therapeutic efficacy [6–9]. A similar framework is being adopted for CTE [5].

A number of potential neuroimaging biomarkers for CTE have been identified (e.g., volumetric magnetic resonance imaging [MRI], diffusion-tensor imaging [DTI], MR spectroscopy) [5], but none of these methods assess the pathology underlying CTE, i.e., p-tau burden. Positron-emission tomography (PET) tau-specific radioligands have emerged as an optimal biomarker for detecting tauopathies, like AD [6,10], with the expectation that PET imaging will serve as the gold standard diagnostic biomarker for CTE. The pragmatism of PET imaging, however, is problematic as it is expensive, time demanding, and involves exposure to radiation. Cerebrospinal fluid (CSF) protein markers of neurodegeneration (e.g., total tau [t-tau] and p-tau) are a practical alternative to PET imaging that is an accepted diagnostic tool in AD [6,11,12]. CSF protein analysis still requires a lumbar puncture, a procedure that is often viewed as invasive, and is feared by many patients.

The development of ultrasensitive blood immunoassays makes it now possible to detect low abundance proteins, such as tau, in the periphery. Blood analysis of tau protein is a time efficient, noninvasive, and reliable procedure, making it a candidate screening biomarker for neurodegenerative tauopathies, such as AD [11,13–17]. Plasma exosomal tau has recently been proposed as a biomarker for CTE [18], but the techniques for isolation of brain-derived exosomes in blood are technically challenging and can lead to significant variability in the quality (e.g., purity, efficiency) of the extracted exosome [19]. Plasma tau is a more appealing option to the clinician and clinical researcher. Plasma assays of p-tau are still being developed and refined. However, plasma t-tau has been supported as a diagnostic tool for AD [6,11,20–22] but not without conflicting reports [23]. It has been theorized that significant axonal damage is required before peripheral increases in t-tau are observed in participants with AD [21].

Because tau is predominantly expressed in neuronal axons [24], plasma t-tau may be sensitive to the diffuse axonal injury that occurs during concussion [25] and RHI [26–30]. The utility of plasma t-tau in the setting of head trauma and RHI exposure is beginning to be explored. In a multicenter cohort study of professional Swedish ice hockey players [31], plasma t-tau concentrations were found to be elevated after a concussion and correlated with duration of postconcussion symptoms. Military personnel with a self-reported traumatic brain injury (TBI) also exhibited higher concentrations of plasma t-tau relative to controls, and plasma t-tau levels were higher for those with a medical record history of TBI and for those with three or more TBIs versus fewer than three TBIs [32]. Greater total postconcussive symptoms correlated with higher peripheral t-tau concentrations [32]. Regarding RHI, increases in plasma t-tau have been reported in a sample of 30 Olympic boxers immediately after a bout where there were no knock-outs [33], providing evidence for the acute effects of RHI on plasma t-tau levels. Exposure to RHI may also lead to chronic elevations in plasma t-tau levels given that RHI-related axonal abnormalities can persist over time [34], have been observed in former NFL players [34–37], and are a common pathological feature in CTE [2].

The potential for plasma t-tau to serve as screening biomarker for CTE remains unknown partially because no study has examined the relationship between RHI exposure and later-life plasma t-tau concentrations. The objective of this study was to examine plasma t-tau concentrations in former NFL players presumably at risk for CTE, compared with same-age controls. In the former NFL group, we investigated the relationship between RHI exposure, using a previously reported cumulative head impact index (CHII) [38], and later-life plasma t-tau concentrations. This study additionally examined the association between plasma t-tau levels and performance on neuropsychological and behavioral/mood tests in the former NFL players. Optimal methodology for identifying a clinical biomarker involves inclusion of a sample with the clinical diagnosis of the disease of interest (suggesting a high probability of disease presence) [39]. Here, CTE is the target disease, but it cannot be diagnosed during life, and the extent of disease and if it is clinically present in the former NFL players are unknown. This is problematic given that significant axonal degeneration may be necessary for plasma t-tau to be elevated [21]. Therefore, one primary objective of this study was to identify a plasma t-tau concentration that had a high specificity to the former NFL group; a highly specific cutoff is one important criterion in the performance evaluation of a biomarker [39].

2. Methods

2.1. Participants

The original sample included 124 subjects (96 former NFL players and 28 same-aged controls) from a study examining in vivo biomarkers for CTE, entitled "Diagnosing and Evaluating Traumatic Encephalopathy Using Clinical Tests" (DETECTs). Recruitment for DETECTs began in 2011 and concluded in 2015. Inclusion criteria for the former NFL players included male, aged 40–69 years, a minimum of two seasons in the NFL and a minimum of 12 years of organized football, and had self-reported complaints of cognitive, behavioral, and/or mood symptoms at the time of telephone screen. Former NFL players must also not have had a history of concussion within one year before study entry. The same-age control group was required to have no history of participation in contact sports, service in the military, self-reported TBI or concussion, or cognitive, behavioral, and/or mood symptoms at telephone screen. Exclusion criteria for all participants included general MRI and/or lumbar puncture contraindications, presence of another central